

# **Synthesis and transformations of $\beta$ -nitroacetamides: Nef reaction and radical cyclisations**



A thesis presented by

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I, Emily S J Gascoigne confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed .....

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## Abstract

This thesis details the investigations into the synthesis and further applications of  $\beta$ -nitroacetamides. The introductory chapter describes the initial discovery and development of the nitro-Mannich reaction, and its extension to the diastereo- and enantioselective formation of  $\beta$ -nitroamines and their derivatives. The use of the nitro functional group as a synthetic handle for the transformation of  $\beta$ -nitroamines and their derivatives is then described, with particular emphasis on reduction, Nef reaction and radical removal of the nitro group.

The results and discussion section focusses on the formation of  $\beta$ -nitroacetamides via the deprotonative or conjugate addition nitro-Mannich reaction, and the subjection of these products to the Nef reaction, and towards radical denitration and *in situ* carbon-carbon bond formation. A wide variety of Nef reactions are described: base/acid hydrolysis, base/oxidation and reductive methods. Nef reactions using base were found to be incompatible with  $\beta$ -nitroacetamides due to an elimination reaction, however a reductive Nef reaction using  $\text{CrCl}_2$  effected the partial reduction of the nitro group to an oxime. Further attempts to reduce the oxime to the corresponding carbonyl functional group were unsuccessful. Nef reaction of  $\beta$ -nitroamines were also unsuccessful, mainly resulting in decomposition.

Initial radical investigations found that a significant excess of tributyltin hydride was necessary for adequate conversion to the denitrated product. It was found that reaction in toluene can lead to the decomposition of  $\beta$ -nitroacetamides. A range of novel  $\beta$ -nitroacetamides with an intramolecular alkenyl- or alkynyl tether were synthesized. Cyclisations of the  $\beta$ -nitroacetamides were successful in most cases, undergoing 5-*exo*-trig cyclisation to give the desired cyclopentyl or indanyl structures. Diastereoselectivity was low, with 2 or 3 of 4 possible isomers observed in many cases. Radical 1,4-translocation of a phenyl group was observed in several cases. Intermolecular radical addition to acrylonitrile was also achieved in good yield in the case of a more activated (benzylic)  $\beta$ -nitroacetamide.

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*For June and For Doris*

Experience: that most brutal of teachers. But you learn, my God do you learn.

– C. S. Lewis

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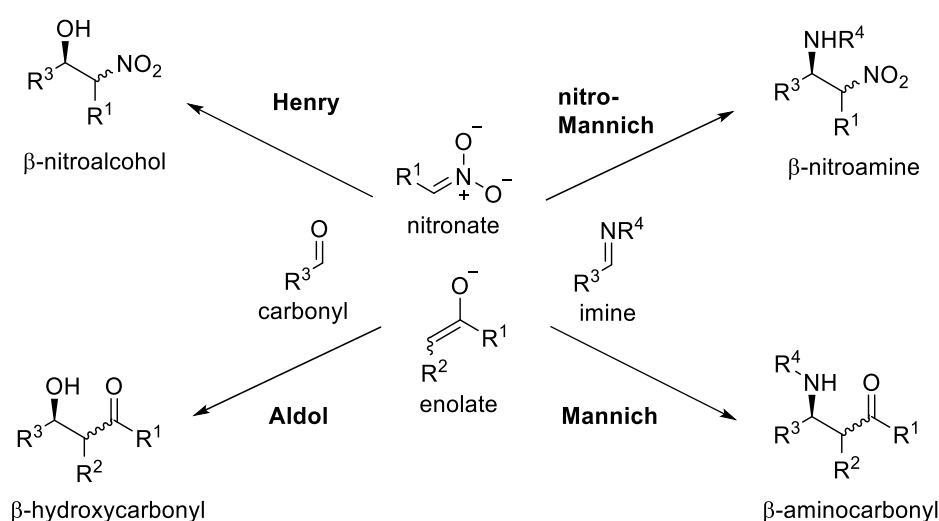
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## Chapter 1. Introduction

### 1.1 The nitro-Mannich reaction

#### 1.1.1 Overview

The synthesis of complex molecules relies on continual innovation and development of new carbon-carbon bond building reactions. The installation of dense functionality in the minimum number of steps is desirable, and the joining together of complex molecular fragments in a single step is very powerful. An important reaction framework is the addition of an active C-H nucleophile to a C=X  $\pi$ -bond partner. A number of methodologies fall under this scope, including the Aldol,<sup>1</sup> Mannich,<sup>2</sup> Henry (nitro-aldol)<sup>3</sup> and nitro-Mannich (aza-Henry)<sup>4</sup> reactions (**Scheme 1**). The nitro-Mannich has seen a recent increase in popularity since the watershed development of stereoselective methodology,<sup>5</sup> before which it had been relatively neglected since its discovery over 100 years ago.<sup>6</sup>

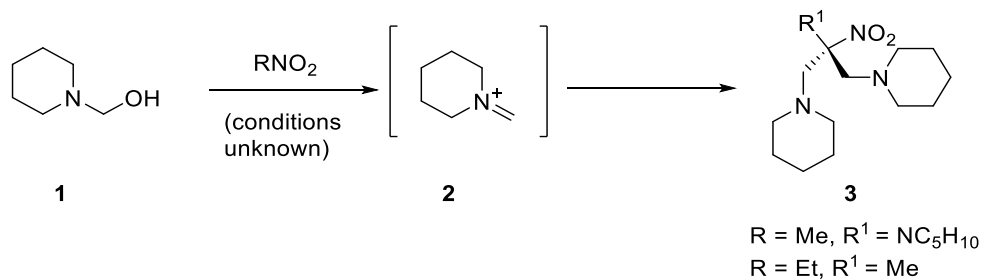


**Scheme 1.** Additions of C-H nucleophiles to C=X  $\pi$ -bonds

The nitro-Mannich reaction is the addition of a nitronate anion to an imine, generating vicinal nitro and amine ( $\beta$ -nitroamine) functional groups. It is important as highly functionalised molecules can be synthesised in a single step; the adjacent nitrogen functional groups are in different oxidation states allowing for selective further manipulation of the molecules. A select review of the literature herein details key nitro-Mannich evolution from its discovery to the present.

### 1.1.2 Initial discovery and early work

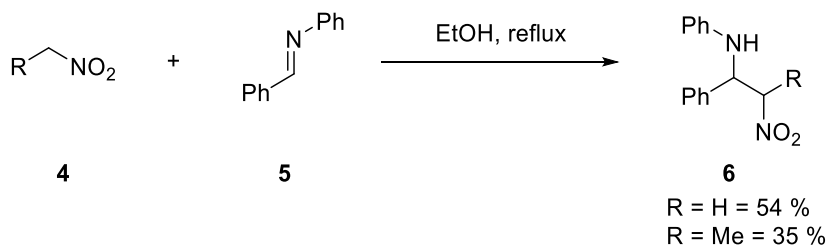
The first nitro-Mannich reaction was reported by Henry in 1896<sup>6</sup> and comprised the addition of short chain nitroalkanes to hemi-aminal **1** derived from piperidine and formaldehyde. The hemi-aminal is thought to lose a molecule of water *in situ* to form iminium ion **2** which undergoes attack from a nitronate species (**Scheme 2**) to give di- or tri-piperidine **3** using nitroethane or nitromethane respectively.



**Scheme 2.** The first reported nitro-Mannich reaction

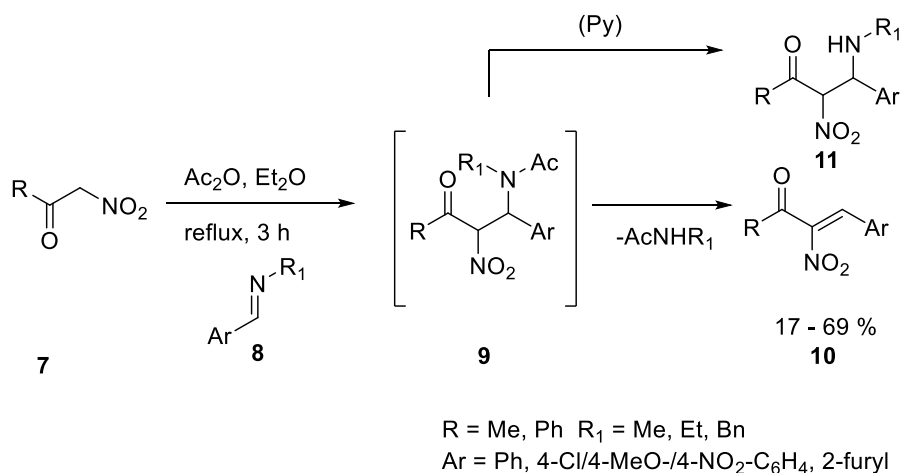
Unfortunately yields and reaction conditions for this transformation are not given, however a rough procedure is given in later work.<sup>7</sup> It was later found that the tri-piperidine product is not formed and that the dipiperidine product is instead the correct product (**3**,  $\text{R}^1 = \text{H}$ ) on reaction of the hemi-aminal with nitromethane.<sup>8</sup> Further developments in the mid-20<sup>th</sup> century mainly focused around the generation of the products of addition of the nitroalkane to two molecules of imine (or iminium ion) generated *in situ* in the reaction from hemi-aminals,<sup>9</sup> formaldehyde<sup>10</sup> and an amine.

The first reported nitro-Mannich reaction using a preformed imine was performed by Hurd in 1950. Refluxing nitromethane or nitroethane in ethanol with benzylideneaniline **5** (**Scheme 3**). The product  $\beta$ -nitroamines **6** were obtained in moderate yields (35 – 54 %) with limited scope and no measure of *dr*.<sup>11</sup>



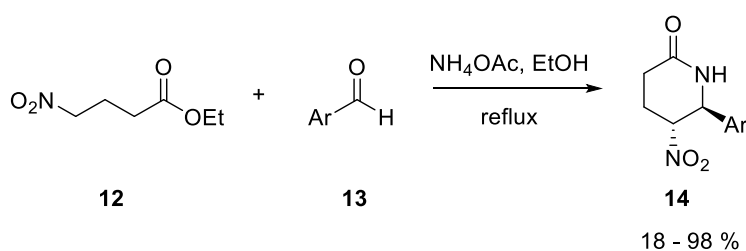
**Scheme 3.** First reported nitro-Mannich reaction using a pre-formed imine

A further report using preformed imines was also detailed, however the product  $\beta$ -nitroacetamides **9** derived from acetylation of the product  $\beta$ -nitroamines proved susceptible to elimination giving nitroalkenes **10** (Scheme 4).<sup>12</sup> It was found that elimination could be avoided by adding pyridine to the reaction to deacetylate the product giving the  $\beta$ -nitroamine **11**.



**Scheme 4.** Elimination of acetamide following the nitro-Mannich reaction

In 1976 the first diastereoselective nitro-Mannich reaction was reported. Reaction of ethyl 4-nitrobutanoate **12** with aromatic aldehydes **13** and ammonium acetate resulted in the formation of 5-nitropiperidin-2-ones **14** via *in situ* cyclisation of the  $\beta$ -nitroamine (Scheme 5). The formation of a ring allowed assignment of the relative stereochemistry of the two chiral centres generated by the reaction as the *anti*-diastereomer by  $^1\text{H}$  NMR.<sup>13</sup>

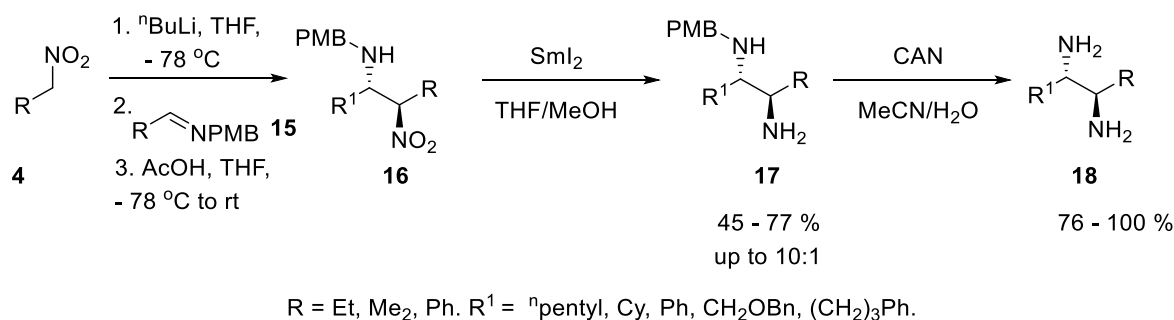


**Scheme 5.** The first diastereoselective nitro-Mannich reaction

### 1.1.3 Non-catalytic nitro-Mannich reactions

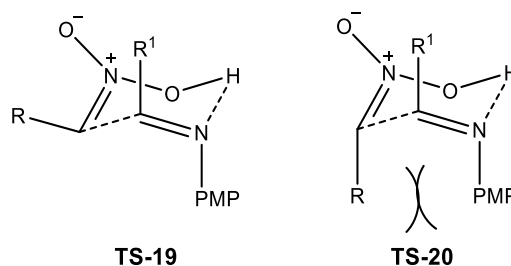
Although the first diastereoselective nitro-Mannich reaction had been performed giving *trans*-5-nitropiperidin-2-ones **14** (Scheme 5) it wasn't until over 20 years later that the first acyclic diastereoselective nitro-Mannich reaction was reported by Anderson *et al.*<sup>5</sup> Deprotonation of a nitroalkane **4** with  $^n\text{BuLi}$  at  $-78^\circ\text{C}$  gave the lithium nitronate, to which

was added *N*-*p*-methoxybenzyl (PMB) imine **15** before quenching with acetic acid at - 78 °C. A range of  $\beta$ -nitroamines **16** were formed in moderate to very good yields (45 – 77 %), with many examples showing a high level of diastereoselectivity (up to 10:1 in favour of the *anti*-diastereomer).



**Scheme 6.** The first acyclic diastereoselective nitro-Mannich reaction

Addition of a nitronate anion to an imine is thermodynamically disfavoured as this results in the formation of the less stable aza-anion (pK<sub>a</sub> ~ 35 cf. nitronate ~ 9).<sup>5</sup> It was found that activation of the imine by acid is necessary for the reaction to occur; addition of acid allowed the reaction to proceed. The nitronic acid formed from initial protonation of the nitronate species has a similar pK<sub>a</sub> to AcOH (4.6 vs 4.7). Presumably the added acid protonates the imine (pK<sub>a</sub> 7 – 9) to promote the reaction with the nitronate species. It was hypothesised that the selectivity arises from a six-membered Zimmerman-Traxler type transition state **TS-19** (**Fig. 1**). A chair cannot form unless the (*E*)-imine is in the axial orientation for the imine lone pair to be protonated **TS-19** or **TS-20**. Steric bulk between R and PMP disfavour **TS-20**, the equatorial R (**TS-19**) is preferred.



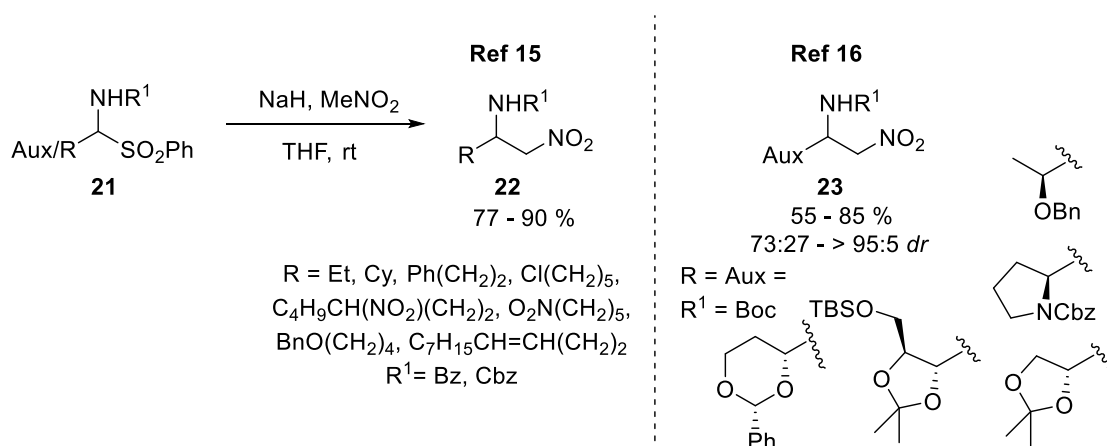
**Fig. 1.** Diastereomeric transition states of the nitro-Mannich reaction

The product  $\beta$ -nitroamines were found to be unstable as they can undergo a retro-nitro-Mannich reaction to regenerate the imine and nitronate anion resulting in decomposition and erosion of the diastereomeric ratio. Reduction of the  $\beta$ -nitroamines by SmI<sub>2</sub> afforded protected 1,2-diamines **17** in satisfactory to good yields, followed by smooth deprotection



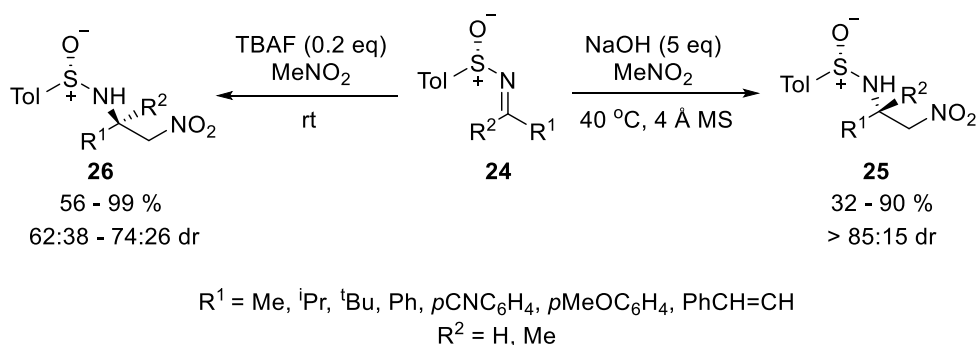
using CAN to give primary 1,2-diamines **18** (Scheme 6).<sup>5</sup> An alternative strategy for the reduction of the unstable  $\beta$ -nitroamines using aluminium amalgam (Al/Hg) followed by H<sub>2</sub> on Pd/C or LiAlH<sub>4</sub> was later described by the same group which negates the use of 7 eq. of the expensive and capricious SmI<sub>2</sub> and in many cases results in a higher yield of 1,2-diamine across two steps.<sup>14</sup>

An alternative nitro-Mannich strategy was published only a year later by Petrini *et al.*<sup>15</sup> Reaction of sodium methanenitronate with imines generated *in situ* from the extrusion of phenylsulfinic acid from amidosulfones **21** under the basic conditions of the reaction afforded  $\beta$ -nitroamines in very good yields (77 – 90 %). An asymmetric diastereoselective variant was performed by the same group in which ‘R’ is a chiral auxiliary (Scheme 7). Bulky ketal groups gave the highest selectivity (up to >95:5 *dr*), and lower selectivity offered by the acyclic OBn centre.<sup>16</sup> The  $\beta$ -nitroamines **23** formed were subjected to the Nef reaction to form the carboxylic ester in high yields (Scheme 60).<sup>15-16</sup>



**Scheme 7.** Diastereoselective nitro-Mannich reaction of enantiomerically enriched amidosulfones with sodium methanenitronate

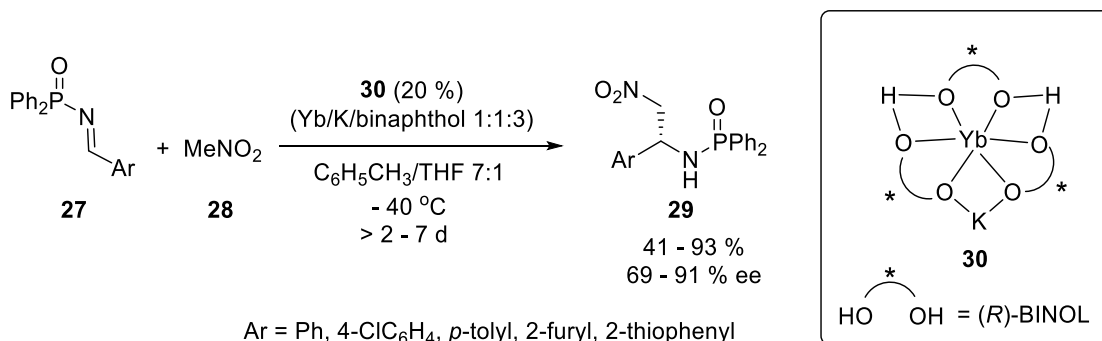
Several other removable chiral auxiliaries have been used in non-catalytic enantioselective nitro-Mannich reactions in which the chiral auxiliary is conveniently incorporated into the imine, including *N*-sulfinyl<sup>17</sup> and *N*-phosphinoyl imines.<sup>18</sup> The first report from the group of Garcia and Cid of the nitro-Mannich reaction of chiral *N*-tolylsulfinyl imines **24** with nitromethane results in the enantioselective formation of tertiary and quaternary stereocentres.<sup>17a</sup> Reaction using NaOH results in the formation of the (*S<sub>S</sub>*, *S*) diastereoisomer **25**. Alternatively, use of catalytic TBAF results in a switch in diastereoselectivity with slight preference for the (*S<sub>S</sub>*, *R*) diastereoisomer **26** (Scheme 8).



**Scheme 8.** Nitro-Mannich reaction using chiral auxiliary *N*-tolylsulfinyl imines

### 1.1.4 Metal-catalysed nitro-Mannich reactions

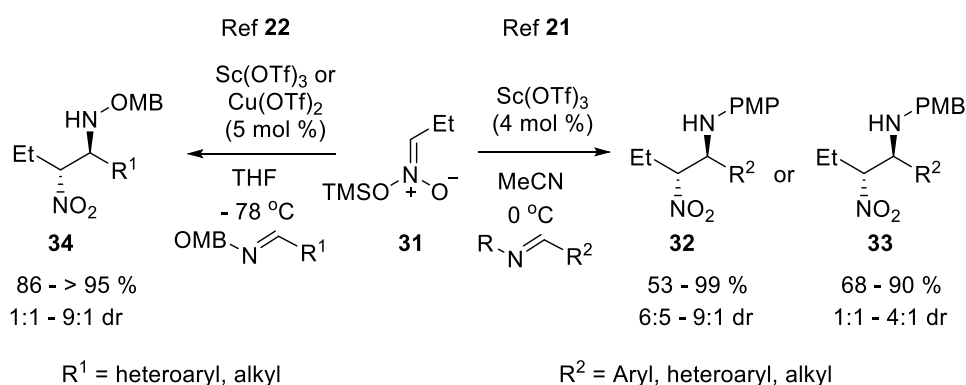
In 1999 the group of Shibasaki became the first to report a metal-catalyzed enantioselective nitro-Mannich reaction. Their methodology utilized a heterobimetallic Yb/K/BINOL (1:1:3, generated from Yb(O<sup>*i*</sup>Pr)<sub>3</sub>, KO<sup>*i*</sup>Bu and binaphthol) catalyst containing both a Lewis acidic and Brønsted basic site to promote the reaction between *N*-phosphinoyl imines **27** and nitromethane **28**, affording the product β-nitroamines **29** in moderate to excellent yields (41 – 93 %) with good enantioselectivities (up to 91 % ee) (**Scheme 9**).<sup>19</sup>



**Scheme 9.** The first metal catalysed asymmetric nitro-Mannich reaction

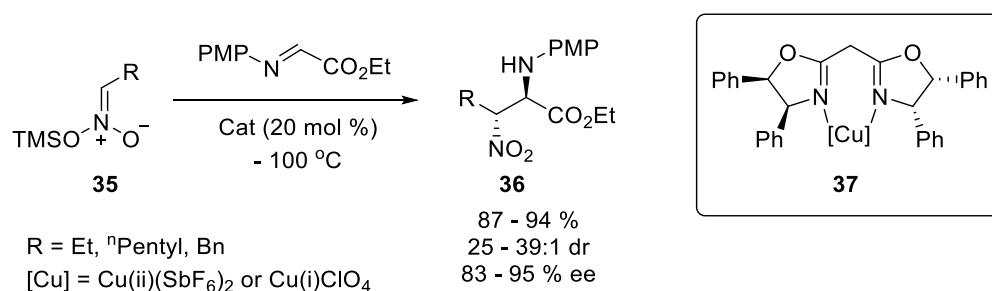
Reaction times were unfortunately long and reaction of higher homologues of nitromethane proved tricky. Switching to an alternative Al/Li/binaphthoxide-KO<sup>*i*</sup>Bu catalyst rectified this, providing β-nitroamines from nitroethane, nitropropane and (3-nitropoxy)benzene in good to excellent yields (68 – 98 %) as the majority *anti*-isomer (3 - 7:1 *dr*) in up to 83 % *ee*. The larger binding pocket of the Al/Li/binaphthoxide-KO<sup>*i*</sup>Bu catalyst is thought to facilitate reaction of the larger nitroalkanes. The reaction is performed under the same conditions as previously with a solvent switch to CH<sub>2</sub>Cl<sub>2</sub>.<sup>20</sup>

A modification of the preliminary nitro-Mannich reaction reported by Anderson<sup>5</sup> was reported in 2000 by the same group detailing the use of a trimethylsilyl nitronate in the nitro-Mannich reaction, catalysed by  $\text{Sc}(\text{OTf})_3$ . This allowed catalytic quantities of Lewis acid to be used (*cf.* stoichiometric quantities needed for reaction of lithium nitronates due to binding of the Lewis acid to the aza anion produced). An improvement in some yields and diastereoselectivity was seen by changing the imine protecting group from *N*-PMB **33** to *N*-PMP **32** (4-methoxyphenyl).<sup>21</sup> A later publication by the same group reported a similar methodology using *N*-OMB (2-methoxybenzyl) imines. A range of alkyl and heteroaryl imines readily formed  $\beta$ -nitroamines **34** in excellent yields (86 - > 95 %) and up to 9:1 dr (**Scheme 10**). Use of  $\text{Ti}(\text{iOPr})_4$  was also successful however in lower yields and diastereoselectivity.<sup>22</sup>



**Scheme 10.** Lewis acid catalyzed nitro-Mannich reaction using TMS-nitronates

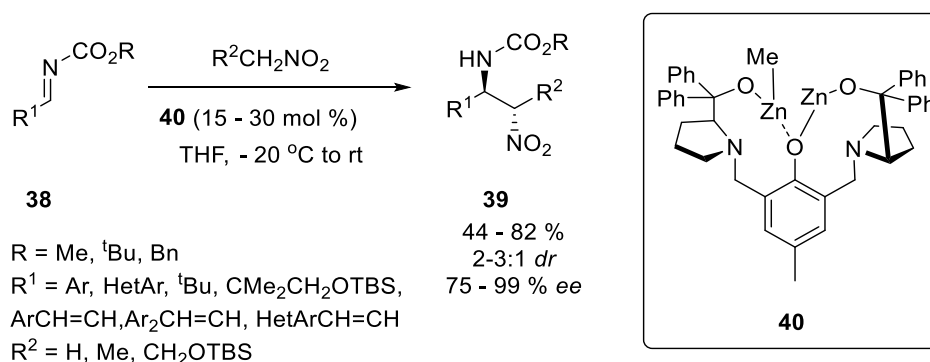
The first reported asymmetric addition of TMS-nitronates to imines using a Lewis acid catalyst was reported shortly after the initial racemic version described above<sup>21</sup> by Jørgensen *et al.*<sup>23</sup> The addition of pre-formed silylnitronates to  $\alpha$ -imino esters afforded  $\beta$ -nitroamines **36** in excellent yields (87 – 94 %) and diastereoselectivities (25:1 – 39:1 *dr*), in 83 – 95 % *ee* using a variety of copper (I)/(II) salts and chiral *cis*-diPh-bisoxazoline (BOX) catalysts **37** (**Scheme 11**).



**Scheme 11.** First asymmetric nitro-Mannich reaction of silyl nitronates

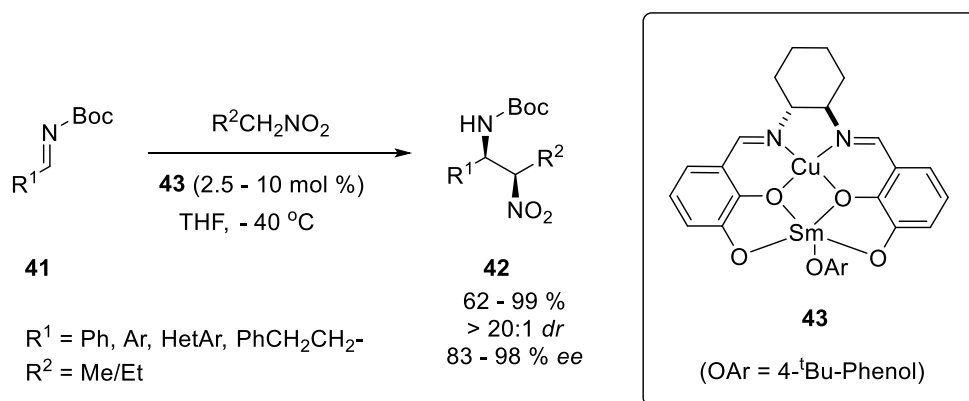
A further report in the same year detailed the direct use of nitroalkanes using triethylamine<sup>24</sup> and BOX catalysts. Improved yields, *dr* and *ee* were seen when switching to a quinine/quinidine base.<sup>25</sup> Unfortunately the reactions were limited to  $\alpha$ -imino esters, presumably this bidentate imine could chelate to the catalytic Lewis acid and aid stereoselectivity.<sup>23-25</sup> However work by Anderson using TMS-nitropropane and a variant <sup>t</sup>Bu-BOX/Cu(OTf)<sub>2</sub> catalyst extended the reaction scope to include aryl and alkyl imines.<sup>26</sup>

Subsequent work by the groups of Palomo,<sup>27</sup> Qian<sup>28</sup> and Trost<sup>29</sup> focused on the use of zinc-based catalysts. In the case of Palomo and Qian, the nitroalkane was limited to nitromethane. Higher homologues were used by Trost, however diastereoselectivity was limited to 2-3:1 (*anti:syn*) however with high *ee* (**Scheme 12**). This represented the first use of unsaturated imines in the nitro-Mannich reaction, in part to avoid side reactions caused by enolisable protons  $\alpha$ -to the imino centre.



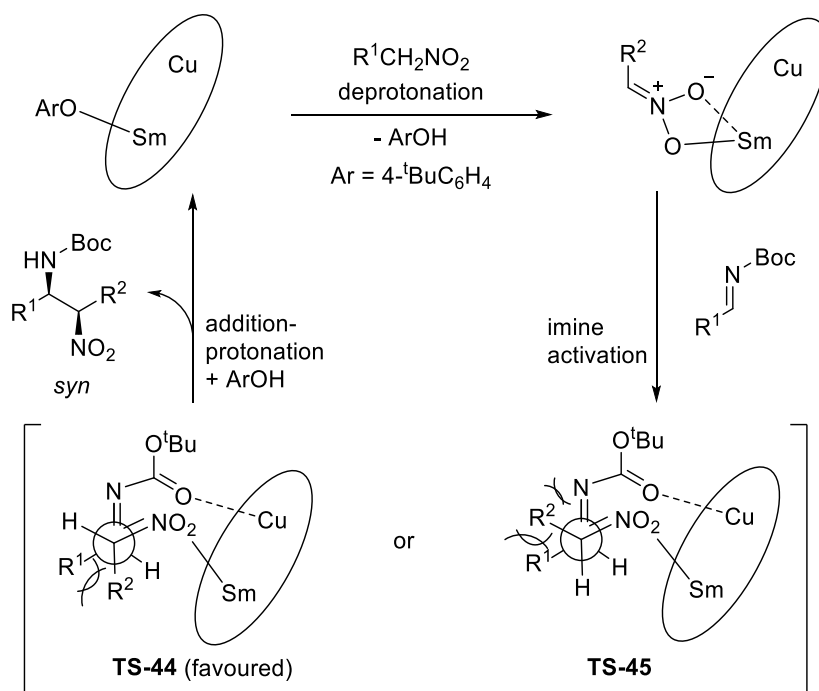
**Scheme 12.** Nitro-Mannich reaction extended to alkene-containing imines using a zinc-based catalyst

An important development in the asymmetric nitro-Mannich reaction is the report of a *syn*-selective nitro-Mannich reaction catalysed by heterobimetallic catalyst **43** from Shibasaki<sup>30</sup> in 2007. Prior to this work, *anti*-selective nitro-Mannich reactions dominated, with this *syn*-selective method providing access to the complementary diastereomer. The Schiff base-Cu(II)/Sm(III) ligand (1:1:1) in the presence of 4-<sup>t</sup>Bu-phenol was found to promote a *syn*-selective reaction between *N*-Boc protected imines **41** and nitroethane/nitropropane in good to excellent yields, diastereo- and enantioselectivities (**Scheme 13**).



**Scheme 13.** First *syn*-selective asymmetric nitro-Mannich reaction

An improved catalyst was reported in 2010, using  $\text{Sm}_5\text{O}(\text{iOPr})_{13}$  in place of  $\text{Sm}(\text{iOPr})_3$  as the lanthanide source and 4-methoxyphenol in place of 4-<sup>t</sup>BuPhenol, the same chiral ligand backbone was used. A wider range of substrates was tolerated, maintaining high *dr*, *ee* and yields.<sup>31</sup> Mechanistic studies were performed, and dual activation of the nitroalkane and imine by the catalyst is thought to account for the *syn*-selectivity. Deprotonation may take place via the Sm-aryl oxide or Schiff base to give a Sm nitronate. In addition, the Cu (II) species can coordinate the imine and control its position in the catalyst with respect to the nitronate.<sup>31</sup> The reaction is thought to proceed via the more favourable **TS-44** transition state (**Scheme 14**), which is less sterically hindered (*c.f.* **TS-45**), protonation of the product by 4-<sup>t</sup>BuPhenol occurs after C-C bond formation to give the *syn*-nitroamine **42**.

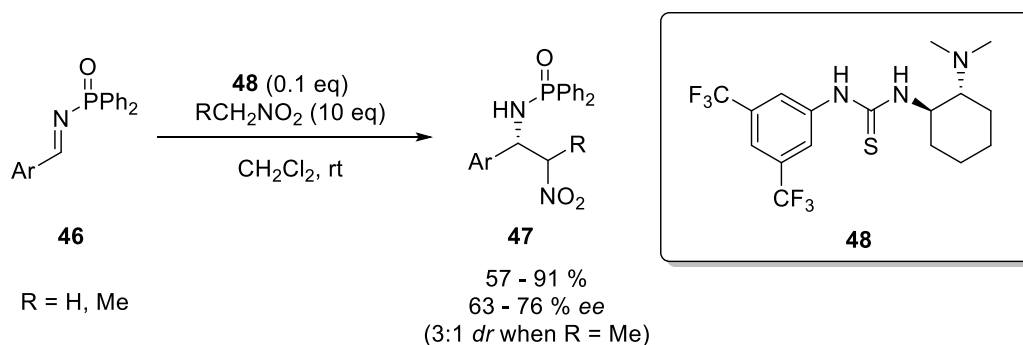


**Scheme 14.** Proposed catalytic cycle in the *syn*-selective metal catalyzed asymmetric nitro-Mannich reaction

### 1.1.5 Organocatalytic reactions

Organocatalysis has become increasingly popular as an alternative for bio- or metal-catalyzed asymmetric reactions since its definition over a decade ago.<sup>32</sup> Using organic molecules as catalysts is often more desirable as they are usually robust and non-toxic, easy to synthesise, and reaction conditions are milder compared to metal-catalyzed equivalents. In particular, they are usually air- and moisture-stable and do not require anaerobic reaction conditions which can be difficult and time consuming.<sup>33</sup> A variety of organocatalytic methods exist but these can be divided into two main types of interaction: covalent or non-covalent. Organocatalysts have been applied to a wide variety of known reactions giving excellent selectivities.<sup>34</sup>

The first reported organocatalyzed nitro-Mannich reactions were reported in 2004 almost simultaneously, by Takemoto<sup>35</sup> and Johnston.<sup>36</sup> Based on the successful thiourea catalysis of an asymmetric Michael addition of malonates into nitroolefins,<sup>37</sup> Takemoto detailed the use of thiourea catalyst **48** for the addition of nitromethane (and one example of nitroethane, 3:1 *dr*, unknown diastereoselectivity) to *N*-phosphorinyl imines **46** (Scheme 15). The reaction proceeded in good to excellent yields (57 – 91 %) and with moderate enantioselectivities (63 – 76 %).<sup>35</sup>



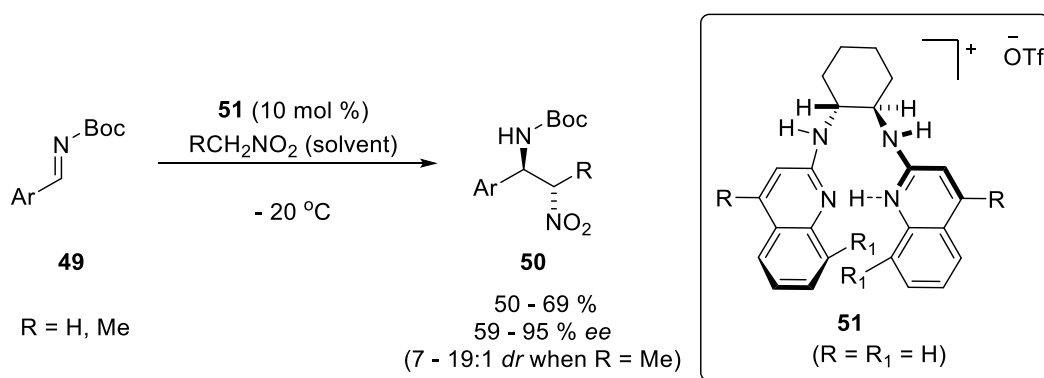
**Scheme 15.** The first asymmetric organocatalyzed nitro-Mannich reaction

Incorporating a basic site into the thiourea catalyst allows for simultaneous activation of both the imine and nucleophile. A couple of years later Takemoto provided an improved procedure extending nitroalkane scope and replacing *N*-phosphorinyl imines with *N*-Boc imines.<sup>38</sup>

In contrast to the work of Takemoto, Johnston *et al.* performed a Brønsted acid organocatalytic reaction using chiral proton bisamidine (HQuinBAM) catalyst **51** (Scheme 16).<sup>36</sup> Protonation of the catalyst by TfOH gives the triflate salt; this avoids a

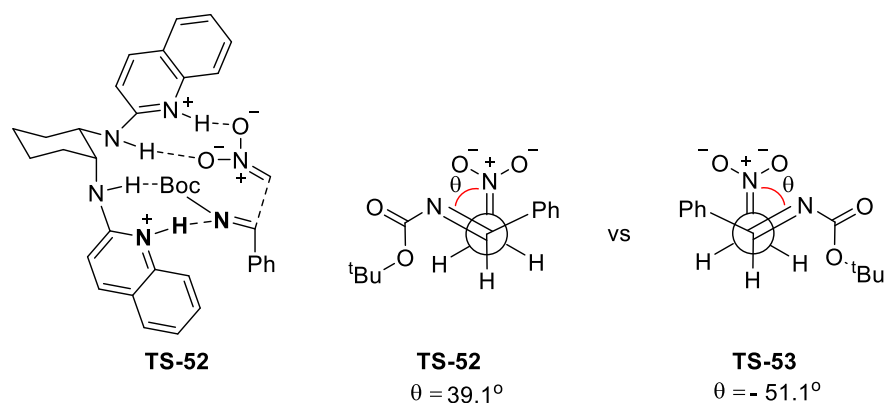
competing achiral acid catalysis pathway. The reaction proceeds with moderate yields (50 – 69 %) and good to excellent *dr* (up to 19:1), enantioselectivity is highest for electron poor aromatic groups, however *ee* drops significantly when Ar = Ph.<sup>36</sup>

Improvements in Johnston's protocol were later reported. Modification of the quinoline section of the catalyst by replacing R with a pyrrolidine ring increased the Brønsted basicity of the catalyst (**51**- R = Pyrrolidine).<sup>39</sup> Electron releasing OMe groups placed in the 8-position of the quinoline provide further increases in reactivity and selectivity attributed to the increase in steric bulk (**51**- R = pyrrolidine, R<sub>1</sub> = OMe).<sup>40</sup>



**Scheme 16.** Organocatalytic nitro-Mannich reaction using a chiral bisamidine proton catalyst

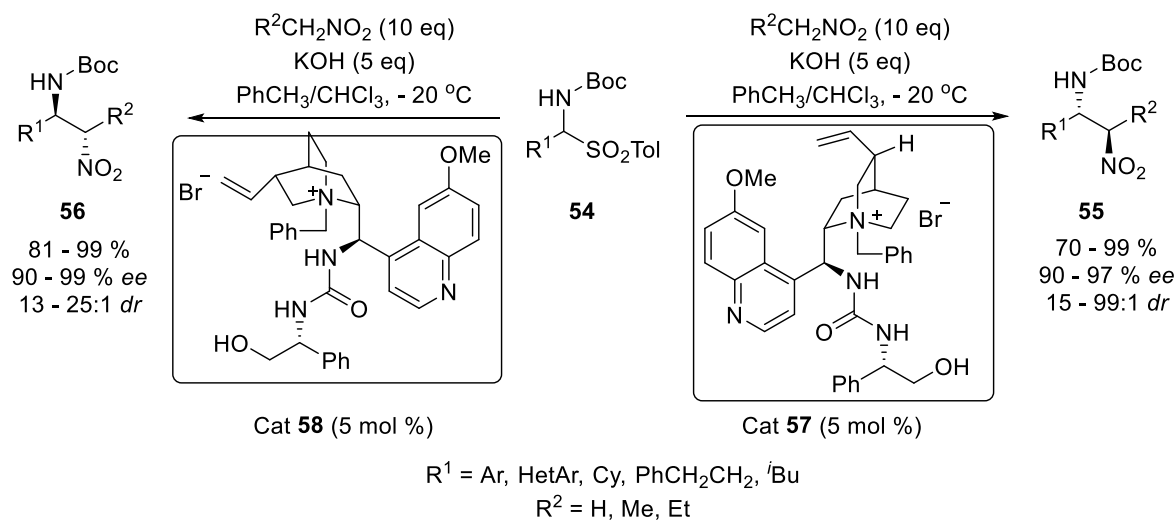
Mechanistic studies<sup>41</sup> suggest primary coordination of the *N*-Boc imine to the protonated quinoline, followed by rate determining deprotonation of the nitroalkane by the free quinoline nitrogen. Hydrogen bonding of both the imine and nitromethane by the organocatalyst results in a lower energy transition state (vs no coordination or mono-coordination of imine or nitromethane). Enantioselectivity is accounted for by formation of a homonuclear positive charge assisted hydrogen bond ((+)-CAHB, N<sup>+</sup>-H...N) between the imine nitrogen and the protonated quinoline nitrogen (**TS-52**). The imine is preferentially held by this (+)-CAHB into a synclinal interaction ( $\theta = 39.1^\circ$ ) with the nitronate **Fig. 2**). Secondary overlap between the nitronate oxygen and imine *N*-Boc carbonyl antibonding orbital further stabilises the transition state.



**Fig. 2.** Enantiotopic transition states in the asymmetric organocatalytic homonuclear positive charge assisted hydrogen bond

A range of organocatalysts have been developed to promote the asymmetric synthesis of  $\beta$ -nitroamines via the nitro-Mannich reaction, further to those mentioned others include guanidines,<sup>42</sup> and phase transfer catalysts.<sup>43</sup> Hydrogen bonding interactions between the catalyst and substrates lead to activation of the imine and/or nitroalkane, and also account for the selectivity of the reaction, governing the approach of the nitronate to the imine.<sup>36, 38, 41, 43a, 44</sup>

Excellent diastereo- and enantioselectivity using cinchona-derived phase transfer catalysts **57** and **58** was recently reported for the addition of nitroalkanes to imines derived *in situ* from  $\alpha$ -amidosulfones (**Scheme 17**).<sup>43a</sup> Use of  $\alpha$ -amidosulfones **54** is beneficial as they negate the problems associated with the corresponding *N*-Boc imines: tautomerisation to enamines and susceptibility to hydrolysis.

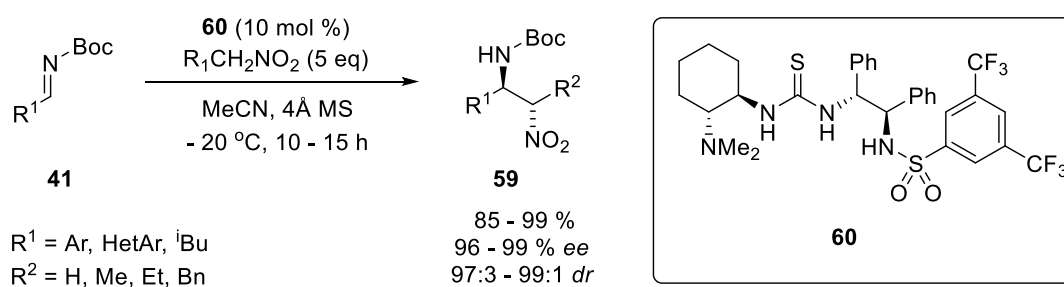


**Scheme 17.** Cinchona alkaloid derived organocatalytic nitro-Mannich reaction



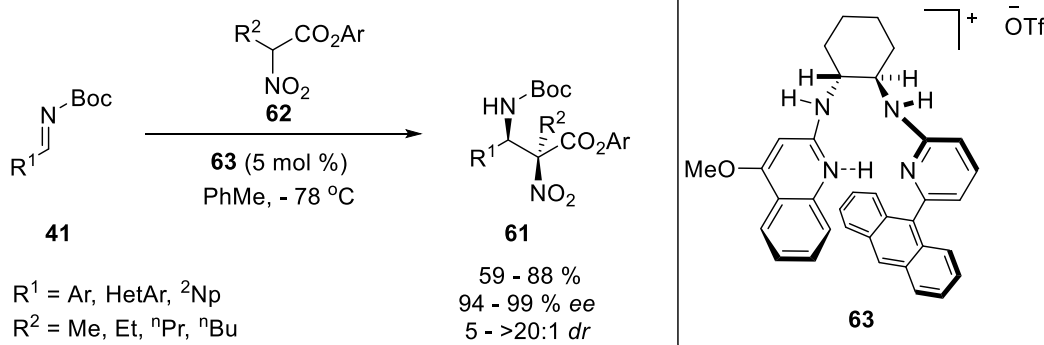
Similar work by Palomo<sup>43b, c</sup> and Herrera<sup>44</sup> was previously reported however the newer work provides both enantiomers of the  $\beta$ -nitroamines in high yields, enantioselectivities and diastereoselectivities with much shortened reaction times and under milder conditions (**Scheme 17**).

The most successful organocatalyzed asymmetric nitro-Mannich reaction reported details the thiourea catalysed addition of *N*-Boc imines **41** to a variety of nitroalkanes by the group of C. Wang.<sup>45</sup> High yields (85 – 99 %), excellent enantioselectivities (96 – 99 %) and diastereoselectivities (93:7 – 99:1) were obtained using thiourea catalyst **60** (**Scheme 18**). In addition to the common thiourea and basic tertiary amine hydrogen bonding interactions, the sulfonamide N-H is also thought to play an important role, increasing reactivity and selectivity of the catalyst.<sup>45</sup>



**Scheme 18.** Asymmetric thiourea catalysed nitro-Mannich reaction

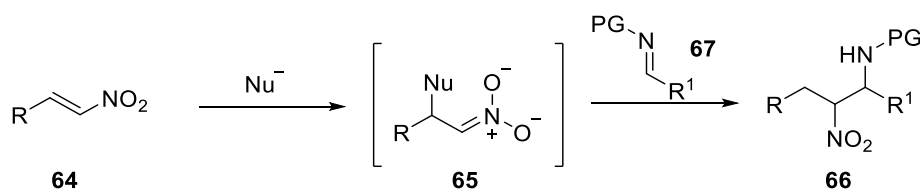
No *syn*-selective asymmetric organocatalyzed nitro-Mannich reactions of secondary nitroalkanes have been reported<sup>46</sup> however *syn*-selective reactions of tertiary nitroacetates **62** forming quaternary  $\beta$ -nitroamides **61** have been reported by Johnston using modified HQuinBAM catalyst **63** (**Scheme 19**).<sup>47</sup> In addition, nitro-Mannich reactions using a zwitterionic organocatalyst have been shown to give the *syn*- $\beta$ -nitroamines as the major product albeit racemically.<sup>48</sup>



**Scheme 19.** Nitro-Mannich reaction to form *syn*-quaternary  $\beta$ -nitroamides **61**

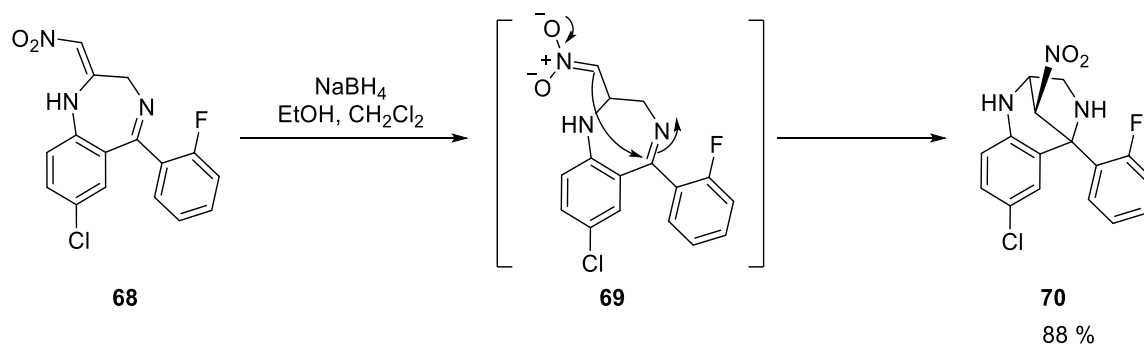
### 1.1.6 The Conjugate addition nitro-Mannich reaction

Michael addition into electron-poor alkenes is an important staple in carbon-carbon chain extension and the formation of carbon-heteroatom bonds. The nitro group is a highly electron withdrawing entity leading to a highly polarised double bond; nitroalkenes are therefore potent Michael acceptors. Nitroalkene synthesis via nitration of alkenes or the Henry reaction makes them valuable in synthesis as precursors to nitroalkanes of which synthesis may be less trivial.<sup>49</sup> Nucleophilic addition to nitroalkenes **64** also leads to the generation of a nitronate **65** without recourse to deprotonation of the corresponding nitroalkane (**Scheme 20**). The scope of 1,4-additions to nitroalkenes is expectedly large, hence this chapter will focus solely on conjugate addition-nitro-Mannich reactions; for information on conjugate additions to nitroalkenes reviews are available.<sup>49-50</sup>



**Scheme 20.** The conjugate addition nitro-Mannich reaction

The first documented conjugate addition nitro-Mannich reaction of a nitroalkene by Walser in 1978 was the result of unexpected intramolecular cyclisation during imine reduction in the synthesis of benzodiazepines (**Scheme 21**).<sup>51</sup>

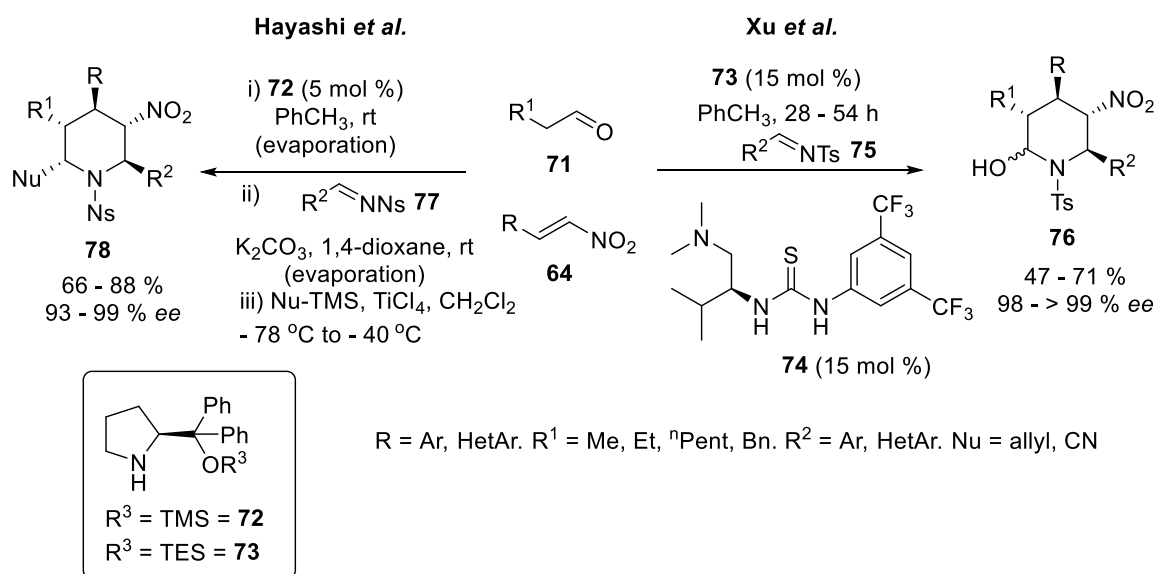


**Scheme 21.** In-situ intramolecular nitro-Mannich reaction of a reduced nitroalkene

The nitroalkene is preferentially reduced by the borohydride, leading to *in situ* formation of nitronate **69**, which spontaneously undergoes 5-*endo*-trig cyclisation on to the imine to form bridgehead nitromethine **70** in good yield (88 %).

### 1.1.6.1 Conjugate addition-cascade reactions of carbon nucleophiles

A number of similar conjugate addition/nitro-Mannich/hemi-aminalisation cascade reactions of carbon nucleophiles were reported in 2010 by Xu,<sup>52</sup> Hayashi<sup>53</sup> and Barbas III.<sup>54</sup> These reactions involve 1,4-addition of aldehydes to nitroalkenes using proline or thiourea catalysis generating a nitronate anion *in situ*. Protonation of the nitronate under the reaction conditions requires a base for continuation of the cascade and in some cases a second catalyst for the nitro-Mannich step is required.



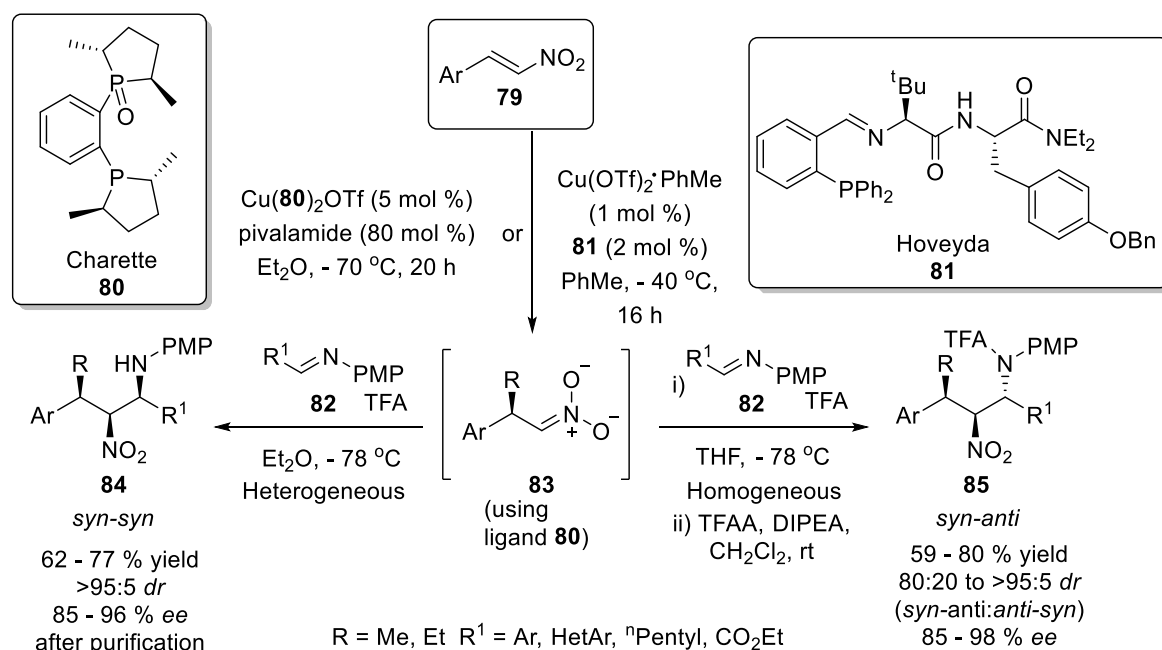
**Scheme 22.** Asymmetric organocatalyzed cascade conjugate addition/nitro-Mannich/lactamisation reactions by Xu and Hayashi

The conjugate addition by Xu was catalysed by proline derivative **73**, followed by thiourea **74** catalysed nitro-Mannich reaction of the intermediate nitroalkane with imine **75** to afford hemiaminal product **76**. Despite the excellent diastereo- and enantioselectivities (> 99 % *ee* for all except one example) achieved, the moderate yields and long reaction times were disappointing.<sup>52</sup> Higher yields were achieved by Hayashi, and Lewis acid catalysed addition of a TMS-allyl or TMS-CN nucleophile to the hemiacetal results in further derivatisation of the piperidine ring. A downfall of the procedure is the requirement to switch solvents between steps i, ii and iii (**Scheme 22**).<sup>53</sup> A similar procedure by Barbas III used  $\alpha$ -OTBS aldehydes and a thiourea catalyst followed by 1,1,3,3-tetramethylguanidine and acetic acid-promoted nitro-Mannich reaction, however yields were significantly lower than those of Xu and Hayashi.<sup>54</sup>

### 1.1.6.2 Conjugate nitro-Mannich reactions with *in situ* trapping of the nitronate anion

#### 1.1.6.2.1 Carbon nucleophiles

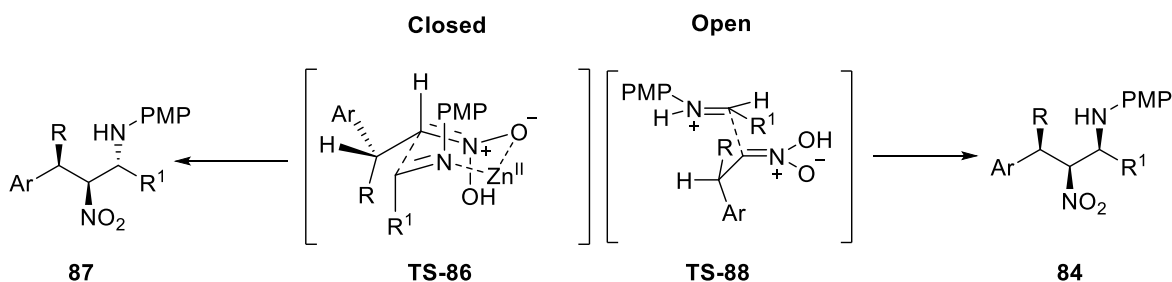
Despite the benefits of the one-pot nitro-Mannich reactions described above, the need to re-form the nitronate following protonation of the original Michael addition product is wasteful. To maximise the utility of the conjugate addition nitro-Mannich reaction, direct use of the nitronate formed *in situ* would be desirable. In 2011, Anderson *et al* reported the first asymmetric acyclic conjugate addition nitro-Mannich reaction via *in situ* trapping of a nitronate (**Scheme 23**).<sup>55</sup> The copper catalysed addition of dialkyl zinc reagents to nitroalkenes in the presence of Charetté ligand **80**<sup>56</sup> or Hoveyda ligand **81**<sup>57</sup> provided enantio-induction for formation of both enantiomers of transient nitronate **83** (**Scheme 23** – nitronate shown from using Charetté ligand **80**). Moderate to good yields (59 – 80 %) were obtained with very good to excellent diastereo- (> 80:20) and enantioselectivities (85 – 98 %). A mixture of 3 of a possible 4 diastereoisomers were formed in the reaction: *syn-anti* **85**, *syn-syn* **84** and *anti-syn*. The *anti-anti* diastereo-isomer was only observed in one case.



**Scheme 23.** Asymmetric and diastereoselective copper catalysed addition of dialkylzincs to nitroalkenes followed by trapping with an imine

Diastereoselectivity was found to be highly dependent on the nature of the solvent used in the nitro-Mannich step. Use of strongly Lewis basic solvents (e.g. THF, DME) resulted

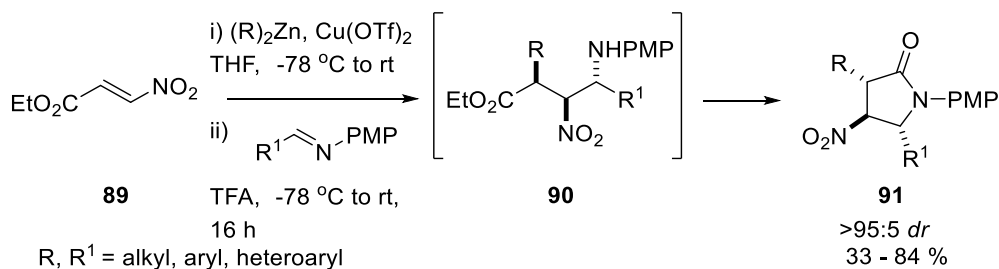
in formation of the *syn-anti* diastereomer and use of less coordinating solvents (e.g. Et<sub>2</sub>O, PhMe) favoured the *syn-syn* diastereomer. The solvent is thought to play an important role in the solubilisation of the zinc (II) trifluoroacetate formed on addition of TFA to the reaction mixture. The zinc (II) trifluoroacetate is soluble in THF, facilitating coordination of the nitronate to the imine in a closed Zimmerman-Traxler type chair conformation **TS-86** leading to the usual *anti*- type nitro-Mannich product **87**. Precipitation of zinc (II) trifluoroacetate when less Lewis basic solvent (Et<sub>2</sub>O, PhMe) is used removes the Zn<sup>2+</sup> species and hence the chair transition state (**TS-86**) does not form.



**Scheme 24.** Open vs closed transition states in the nitro-Mannich reaction after dialkyl zinc addition

In lieu of **TS-86** an open transition state can occur in which approach of the nitronate to the imine is staggered with opposing dipoles; minimisation of steric interactions therefore determines **TS-88** as the most likely conformation and this leads to the observed *syn-syn* product **84**.<sup>55</sup> A notable exception to this being reactions proceeding in a homogeneous fashion despite using a less coordinating solvent, this was observed when R<sup>1</sup> = CO<sub>2</sub>Et in PhMe. In this case, the Zn<sup>2+</sup> species is in solution and presumably a six-membered TS can form hence the *syn-anti* isomer **87** was formed.

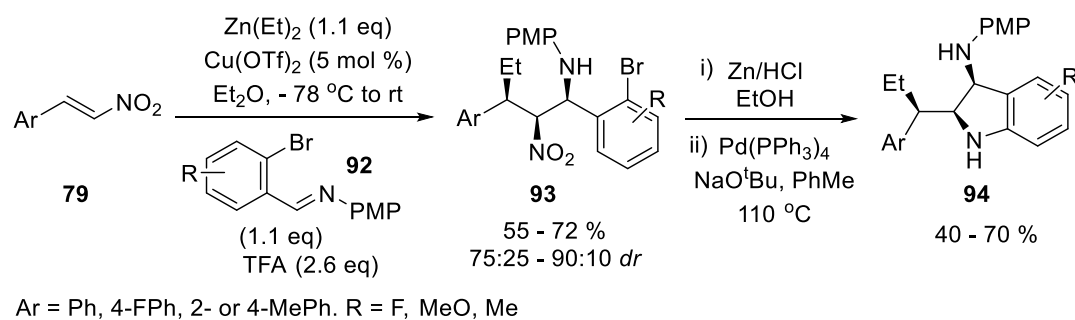
The procedure was further elaborated by Anderson with the introduction of ethyl nitroacrylate as the nitroalkene partner.<sup>58</sup> Access to highly substituted pyrrolidin-2-ones **91** was effected on warming the reaction mixture containing the product β-nitroamines **90** from – 78 °C due to spontaneous intramolecular lactamisation. Following from the unexpected homogeneous reaction observed on using ethyl glyoxylate imine,<sup>55</sup> (**82**, R<sup>1</sup> = CO<sub>2</sub>Et, **Scheme 23**) reaction of nitroacrylate **89** in either class of solvent is also homogeneous in both THF/Et<sub>2</sub>O and the *syn-anti* isomer is observed in both cases (**Scheme 25**).



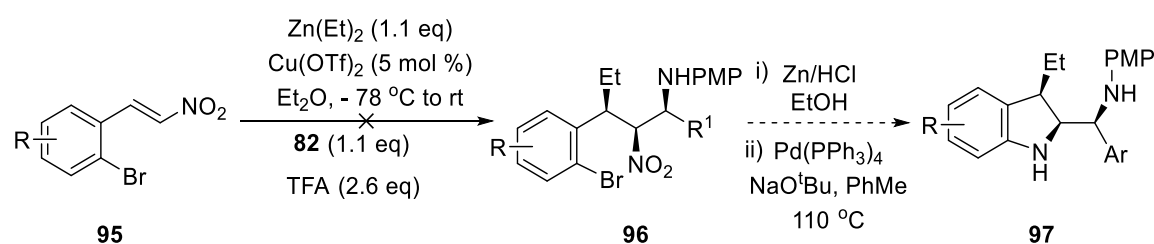
**Scheme 25.** Nitro-Mannich reaction and subsequent lactamisation giving pyrrolidin-2-ones

Racemic addition of a variety of dialkyl zinc reagents proved effective, with a wide range of imine substituents also tolerated in low to high yields (33 – 84 %) and diastereoselectivities (>95:5, *syn-anti* with the exception of *N*-Ts pyrrole, 85:15) (**Scheme 25**). Enantioselective addition of diethyl zinc in the presence of a chiral-Cu catalyst was also achieved, and recrystallization of the product pyrrolidin-2-one afforded the product in 99 % *ee*. An experiment was run in *d*<sub>8</sub>-THF in which the proportion of lactam:open-chain β-nitroamine was investigated by <sup>1</sup>H NMR over time, this revealed the presence of minor diastereoisomers which had not undergone lactamisation. Lactamisation is the rate determining step<sup>59</sup> and occurs slowly upon warming to rt. It is thought that the minor diastereoisomers do not cyclise but instead equilibration of the minor diastereoisomers occurs to give the *syn-anti* diastereoisomer before eventual cyclisation. The *syn-anti* β-nitroamine cyclisation to give the *trans,trans*-pyrrolidin-2-one **91** is favourable as this diastereomer places all substituents in the equatorial position.<sup>58</sup> A preparation of pyrrolidin-2-ones via the nitro-Mannich reaction by Dixon *et al.*<sup>59</sup> was published shortly before this method. However Dixon's method contains some drawbacks. The Dixon method requires pre-alkylation of the nitroalkane which is obviated in a simple dialkyl zinc addition in this procedure. In addition diastereoselectivity in Dixon's procedure was lower (3:1 – 12:1 *c.f.* >95:5) probably due to the higher temperature (70 °C *c.f.* rt) used providing access to a second, less stable isomer.<sup>59</sup>

This methodology has further been extended to produce indolines (**Scheme 26**). A racemic nitro-Mannich reaction is reported for a range of nitroalkenes **79** and imines **92** with moderate to good yields (55 – 72 %) and diastereoselectivities (75:25 – 90:10) in favour of the *syn-syn*  $\beta$ -nitroamine **93**.<sup>60</sup>

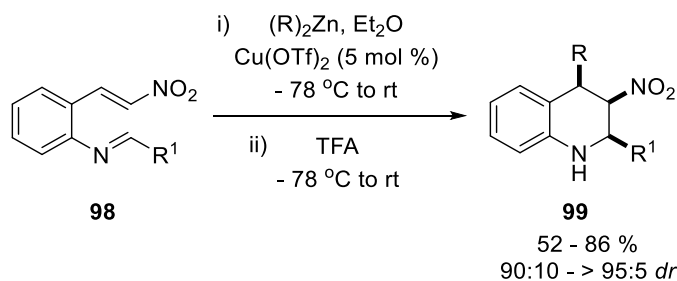


**Scheme 26.** Conjugate dialkyl zinc addition nitro-Mannich reaction and reduction-cyclisation. Reduction of the nitro group with Zn/HCl followed by Buchwald-Hartwig cyclisation effected cyclisation to indolines **94** in moderate to good yields. Unfortunately copper catalysed conjugate addition of diethyl zinc to 2-bromonitrostyrenes **95** proved unsuccessful under a range of conditions (**Scheme 27**), hence only cyclisation of the amine with the imine portion of the molecule is described.<sup>60</sup>



**Scheme 27.** Hypothetical formation of indolines **97** via diethyl zinc addition to nitroalkenes **95**

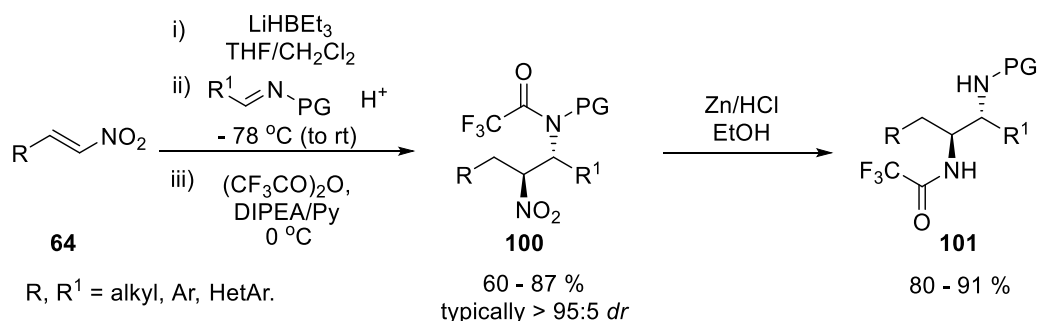
Addition of diethyl zinc to nitrostyrenes containing tethered *ortho*- aniline-based imines **98** results in the formation of 2,3,4-trisubstituted tetrahydroquinolines **99** in moderate to good yields (52 - 86 %) and with good to excellent diastereoselectivities (90:10 - > 95:5) (**Scheme 28**). The majority *cis,cis*-diastereoisomer **99** is thought to be derived from the usual *anti*-selective nitro-Mannich six-membered chair transition state.<sup>61</sup>



**Scheme 28.** Nitro-Mannich conjugate cyclisation reaction to form 2,3,4-trisubstituted tetrahydroquinolines

### 1.1.6.2.2. Hydride nucleophiles

The first observed hydride conjugate addition nitro-Mannich reaction by Walser is described above (**Scheme 21**).<sup>51</sup> Until recently little research into the conjugate addition of hydride nucleophiles followed by *in situ* trapping of the nitronate with an imine had been explored. Anderson's conjugate addition nitro-Mannich reaction using dialkyl zincs was expanded to hydride sources the following year.<sup>62</sup> The 1,4-addition of hydride to a nitroalkene followed by nitro-Mannich trapping of the nitronate with an imine (the reductive nitro-Mannich reaction) was effected using Superhydride® to give  $\beta$ -nitroacetamides **100** in good yields (60 – 87 %) and diastereoselectivities (typically 90:10 to > 95:5 *dr*) (**Scheme 29**). Both OMB and PMP imines may be used; however reaction of the PMP imine requires use of the stronger TFA acid, OMB requires only AcOH. This was rationalised to be due to the lower availability of the lone pair in the PMP imine, hence a stronger acid was needed for protonation to occur. Interestingly, reaction of  $\beta$ -nitrostyrenes required the use of TFA in order to solubilise the nitronate and produce a homogeneous reaction mixture. In the absence of TFA, conversion of  $\beta$ -nitrostyrenes was < 5 %, however this rose to 90 % (OMB) or > 95 % (PMP) on switching from AcOH to TFA.<sup>62</sup>



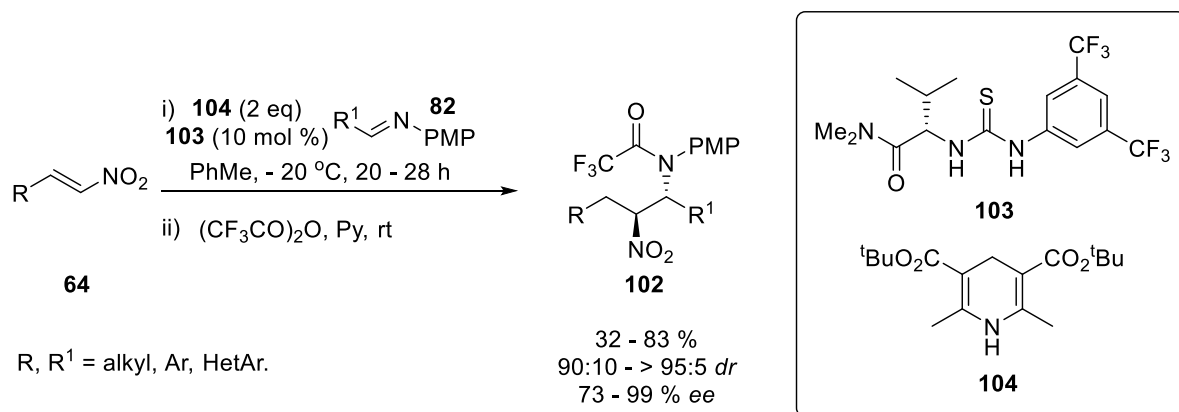
**Scheme 29.** Reductive nitro-Mannich reaction using Superhydride® followed by TFA protection and reduction

Reduction of  $\beta$ -nitroacetamides **100** with Zn/6 M HCl resulted in reduction of the nitro group to an amine in very good yields (80 – 91 %) with translocation of the 2,2,2-trifluoroacetyl group onto the primary amine. These differentially protected 1,2-aminoacetamides **101** may be selectively manipulated, hence are important intermediates in synthesis.

In order to improve the usefulness of the reductive nitro-Mannich reaction, and building on previous knowledge of asymmetric nitro-Mannich catalysis methodology, a year later



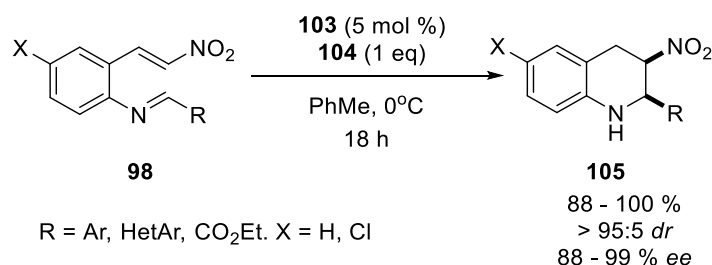
an asymmetric variant was reported by the same group.<sup>63</sup> Hantzsch ester **104** acts as a bulky hydride source; thiourea catalyst **103** was found to effectively promote the reaction to afford  $\beta$ -nitroacetamides **102** in good yields (59 – 81 % excl. R = Furyl), diastereoselectivities (typically > 95:5 *dr*) and excellent enantioselectivities (typically 90 – 99 % *ee*) (**Scheme 30**).



**Scheme 30.** Asymmetric reductive nitro-Mannich reaction

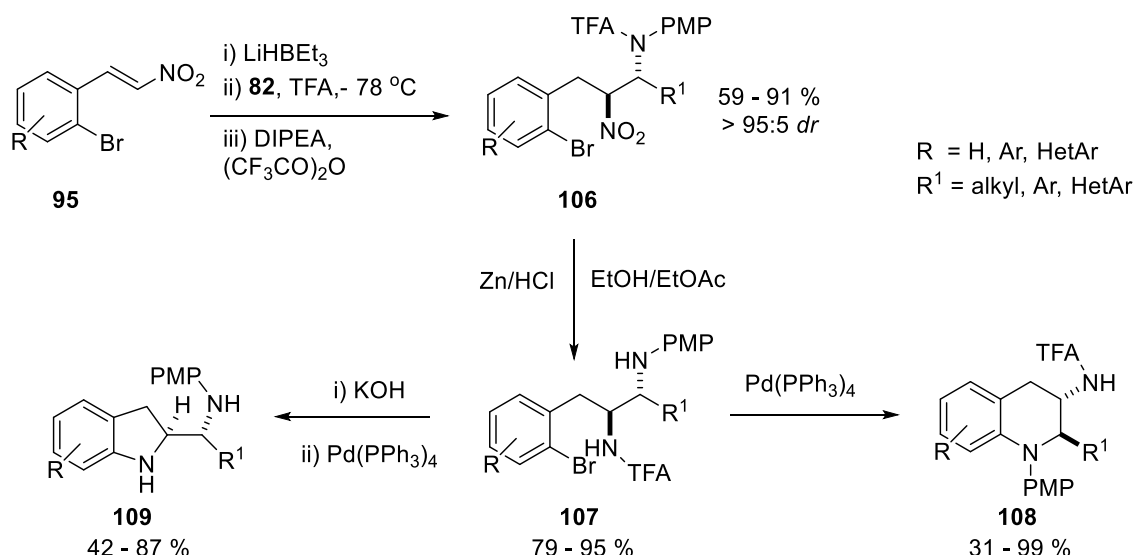
The <sup>n</sup>pentyl imine analogue suffered from instability during the long reaction times at -20 °C, performing the reaction at rt resulted in a drop in *ee*. The furyl- nitroalkene analogue achieved only 32 % yield after 10 d, it was found that where R is electron rich, the reaction was sluggish. As is common in nitro-Mannich reactions, diastereoselectivity is thought to originate from a six-membered chair transition state. Enantioselectivity is hypothesised to be derived from hydrogen-bonding interactions of the imine and nitronate with the thiourea catalyst.<sup>63</sup>

This reductive nitro-Mannich methodology has recently been applied to the synthesis of tetrahydroquinolines **105** from aniline derived imine-tethered nitroalkenes **98** previously mentioned (**Scheme 28**). Slight modification of the reaction conditions results in the formation of tetrahydroquinolines **105** in good to excellent yields (88 – 100 %) diastereoselectivities (> 95:5 *dr*) and enantioselectivities (88 – 99 % *ee*) (**Scheme 31**). A lower catalyst loading was used and only 1 eq Hantzsch ester was required<sup>64</sup> compared to 2 eq used in the enantio- and diastereoselective reaction between nitroalkenes **64** and imines **82** as previously described (**Scheme 30**).<sup>62</sup> Only the *cis*- diastereoisomer was observed, this was thought to be the kinetic product. Epimerisation to the thermodynamic *trans*-diastereoisomer (9:1 *dr*, *trans*:*cis*) takes place upon stirring with DBU in CH<sub>2</sub>Cl<sub>2</sub> for 16 h at rt.



**Scheme 31.** Reductive asymmetric nitro-Mannich cyclisation reaction to form *cis*-disubstituted tetrahydroquinolines

The reductive nitro-Mannich reaction of 2-bromoaryl nitroalkenes **95** was effected using the Superhydride® procedure previously described.<sup>64-65</sup> Protection of the crude  $\beta$ -nitroamines afforded  $\beta$ -nitroacetamides **106** in good to excellent yields (59 – 91 %) as essentially only one (*anti*-) diastereomer after purification (**Scheme 32**).



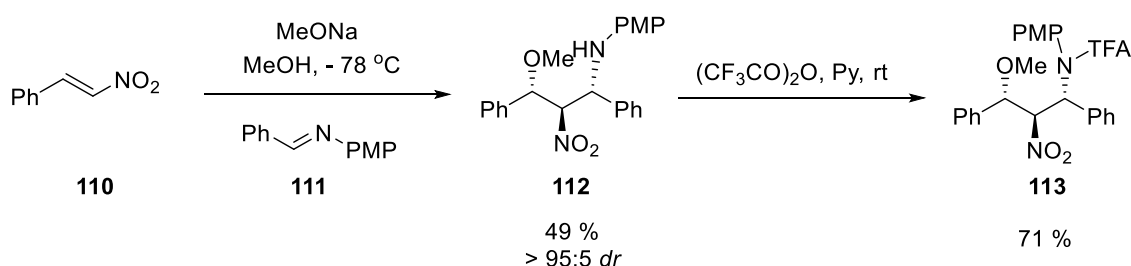
**Scheme 32.** Reductive nitro-Mannich reaction of 2-bromoaryl nitroalkenes, reduction and cyclisation to give nitrogen heterocycles

Reduction of the  $\beta$ -nitroacetamides encountered problems using the previous Zn/HCl method employed<sup>62</sup> due to competing reduction of the C-Br bond. However slight modification of the procedure led to selective reduction of the nitro group and afforded differentially protected 1,2-aminoacetamides **107** in excellent yields (79- 95 %). The orthogonal nature of the *N*-protecting groups rendered the amine more amenable to cyclisation than the trifluoroacetamide due to the higher availability of the nitrogen lone pair. Cyclisation to the *trans*-substituted tetrahydroquinolines **108** was successful in low to excellent yields (33 – 99 %, **Scheme 32**). This provides an alternative stereochemical outcome to the *cis*-tetrahydroquinolines described by the same group.<sup>64</sup> Alternatively,

hydrolysis of the trifluoroacetamide by KOH unmask a primary amine, which upon treatment of  $\text{Pd(PPh}_3)_4$  under very similar conditions underwent Buchwald-Hartwig cyclisation with the now more nucleophilic primary amine to give indolines **109** in moderate to very good yields (42 – 87 %).<sup>65</sup> The lower yields of the indolines may be partly attributed to the instability of some analogues to column chromatography.

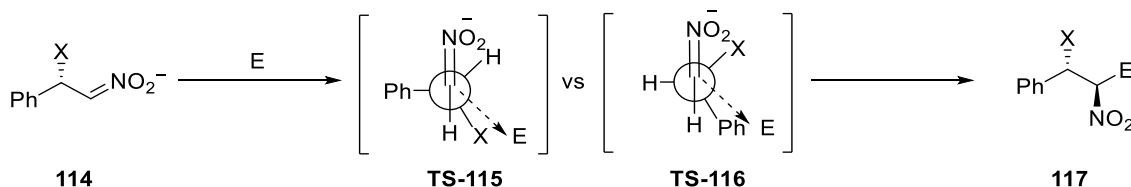
#### 1.1.6.2.3 Heteroatom nucleophiles

The conjugate addition of heteroatom nucleophiles to nitroalkenes followed by trapping with imines has also been investigated.<sup>66</sup> In a range of carbon, nitrogen, oxygen, sulfur and phosphorus based nucleophiles tested by Anderson *et al*, conjugate addition followed by direct trapping of the nitronate with an imine was only possible using NaOMe (Scheme 33).<sup>66a</sup>



**Scheme 33.** Conjugate addition of an oxygen nucleophile to a nitroalkene followed by *in situ* trapping of the nitronate with an imine

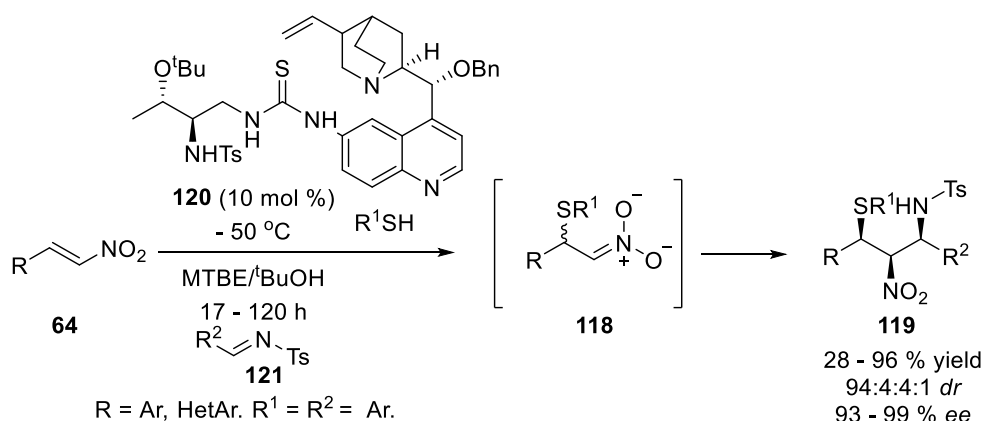
Interesting selectivity was seen in this reaction in the generation of **112** which is the rarely observed *anti,anti*-diastereoisomer.<sup>55</sup> Although the *anti*-configuration of the nitro-Mannich step is well explained, *anti*-addition of the electrophile  $\alpha$ -to the stereocentre is unusual. According to calculations by Houk an electron donating group (in this case Ph or H) must be placed perpendicular to the  $\pi$ -bond of the nitronate to maximise the energy of the  $\pi$ -HOMO (Scheme 34).<sup>66a</sup>



**Scheme 34.** Selectivity in the addition of an electrophile  $\alpha$ -to a stereocentre

In the two possible conformers shown above, **TS-116** was hypothesised to be the most reactive, however **TS-115** is shown experimentally to be more favourable presumably as approach of the electrophile 'E' is less sterically hindered.<sup>66a</sup>

An interesting observation in the light of this mechanism and diastereoselectivity is the observation of Peng *et al* that sulfur-Michael *in situ* nitro-Mannich reactions proceed to form the *syn,syn*-1-amino-2-nitro-3-sulfur compounds **119** in high yields (up to 96 %) diastereoselectivities (up to 91:4:4:1) and in excellent enantioselectivities (up to 99 %) using thiourea **120** (Scheme 35). Only trace amounts of the *anti,anti*- diastereomer (< 5 %) were observed, the remaining diastereomers were also present (< 15 %). Remarkably addition to a nitroalkene under the same conditions described in the absence of an imine results in formation of protonated Michael adduct **118** in only 32 % *ee*. It is thought that under the reaction conditions dynamic kinetic resolution takes place. Reversible addition to the nitroalkene occurs with low enantioselectivity, however, reaction of the (*S*)-adduct then proceeds to react with imine **121** from the *Si*-face.

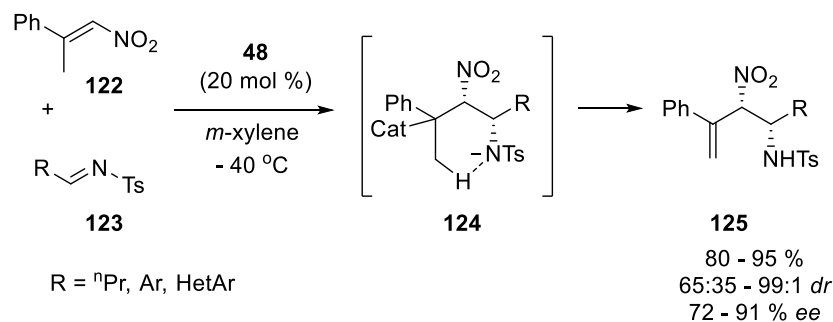


**Scheme 35.** Conjugate addition sulfur-Michael nitro-Mannich reaction

### 1.1.7 Aza-Morita-Baylis-Hillman reactions

Aza-Morita-Baylis-Hillman reactions have also been reported in which 1,4-addition of a nucleophile to a nitroalkene generates a nitronate *in situ*, followed by nitro-Mannich reaction with an imine. The catalyst can then be eliminated, regenerating the nitroalkene.<sup>67</sup> In this case, a proton shift from an adjacent methyl group to the aza-anion **124** occurred after thiourea **48**-catalysed addition of nitroalkene **122** to imine **123**, followed by elimination of the catalyst **48** to afford *exo*-alkene **125**, retaining the  $\beta$ -nitroamine stereocentres (Scheme 36).<sup>68</sup> Catalysis using Takemoto's thiourea catalyst **48** led to an efficient reaction (80 – 95 %), with low to excellent diastereoselectivities favouring *syn*-**125** (65:35 – 99:1 *dr*) in very good enantioselectivities (72 – 91 % *ee*). Formation of the *syn*-product is unusual;<sup>4</sup> the products formed from previous use of

Takemoto's organocatalyst in the nitro-Mannich reaction (**Scheme 15**) was not assigned as the *syn*- or *anti*-diastereoisomer.

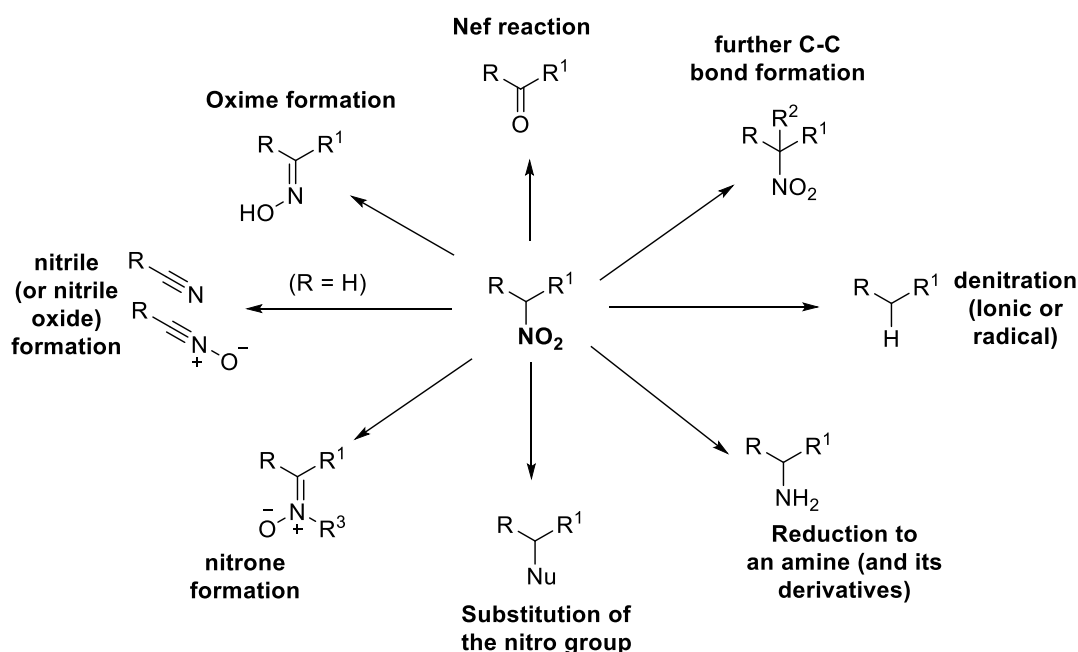


**Scheme 36.** Morita-Baylis-Hillman nitro-Mannich reaction

## 1.2 The nitro group

### 1.2.1 Overview

The nitro group is a highly versatile functional group. Often referred to as a ‘synthetic Chamaeleon’,<sup>69</sup> this describes its ability to act as a masked version of other functional groups (**Fig. 3**).



**Fig. 3.** Some functional group conversions of the nitro group

This is particularly important due to its ability to form carbon-carbon bonds through nucleophilic addition to various electrophiles. Transformations of the nitro group include reduction to amines (and their derivatives),<sup>70</sup> the Nef reaction,<sup>71</sup> conversion to oximes,<sup>72</sup> nitriles,<sup>72g, 73</sup> nitrile oxides,<sup>74</sup> nitrones,<sup>74</sup> substitution<sup>75</sup> or elimination<sup>43c, 58, 76</sup> of the nitro

group.<sup>49a</sup> This is in addition to further carbon-carbon bond formation (**Fig. 3**). A short review of nitro group interconversions is given showcasing  $\beta$ -nitroamines where applicable. Subsequent chapters focus on the Nef reaction and radical denitration hence they will not be discussed here.

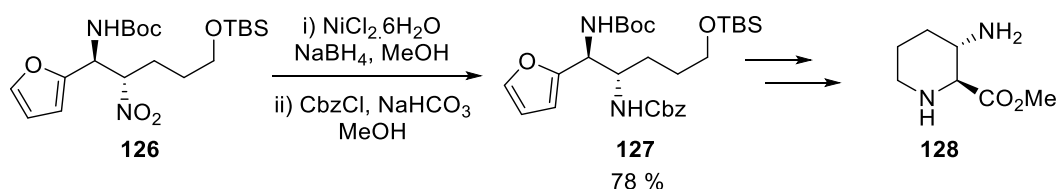
### 1.2.2 Reduction of the nitro group to an amine

Reduction of the nitro group is an important method in the synthesis of amines and their derivatives.<sup>49a, 70a, 70c</sup> A number of methods for this transformation exist, including electrolytic reduction,<sup>77</sup> hydrogenation using transition metal catalysts (Pd/Pt/Ru),<sup>78</sup> use of metals in transfer hydrogenation,<sup>79</sup> dissolving metal or SET reductions (Zn/Fe/Ni/Sn/Sm/Al/Hg).<sup>5, 14, 60, 65, 70b, 80</sup>

#### 1.2.2.1 Reduction of $\beta$ -nitroamines to 1,2-diamines

The reduction of  $\beta$ -nitroamines (or  $\beta$ -nitroacetamide equivalent) to the corresponding 1,2-diamines can be carried out via many different methods. Due to the unstable nature of  $\beta$ -nitroamines to retro-addition and in some cases epimerisation, reductions must be carried out under mild conditions to avoid decomposition. Methods employed to reduce the nitro group include the use of samarium (II) diiodide<sup>19-20, 22, 26, 36, 81</sup> (**Scheme 6**),<sup>5</sup> zinc/acid (**Schemes 26, 29 & 32**),<sup>60, 65, 66b, 82</sup> hydrogenation with Raney nickel<sup>24, 43c, 83</sup> or palladium on carbon,<sup>43c, 84</sup> aluminium amalgam,<sup>14, 65, 85</sup> tin (II) chloride<sup>86</sup> and borides generated *in situ* from sodium borohydride and cobalt<sup>40, 87</sup> or nickel<sup>30-31, 88</sup> (II) chlorides.

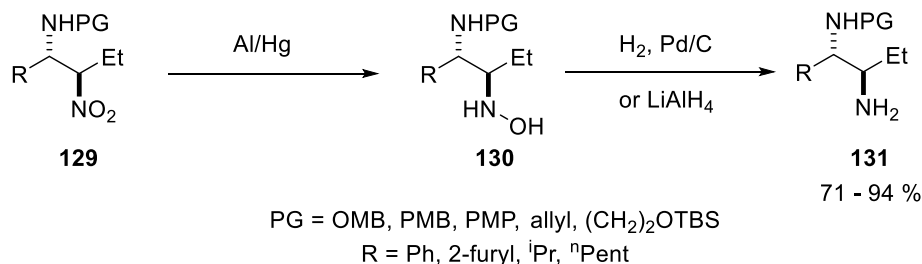
Reduction of *N*-Boc  $\beta$ -nitroamine **126** by nickel boride prepared *in situ* from nickel (II) chloride hexahydrate and sodium borohydride resulted in a good yield of *N*-Boc and *N*-Cbz protected 1,2-diamine **127** (**Scheme 37**). Further manipulation led to methyl 3-aminopiperidine-2-carboxylate **128**.<sup>88a</sup>



**Scheme 37.** Reduction of a  $\beta$ -nitroacetamide with nickel boride

Another example details the use of mild sequential one electron reducing aluminium amalgam (Al/Hg) for reduction of sensitive  $\beta$ -nitroamines **129**. Although reduction

directly to the 1,2-diamines **131** using Al/Hg is known,<sup>85</sup> in the case of  $\beta$ -nitroamines **129** the hydroxylamine **130** was the more significant product (**Scheme 38**).<sup>14</sup>



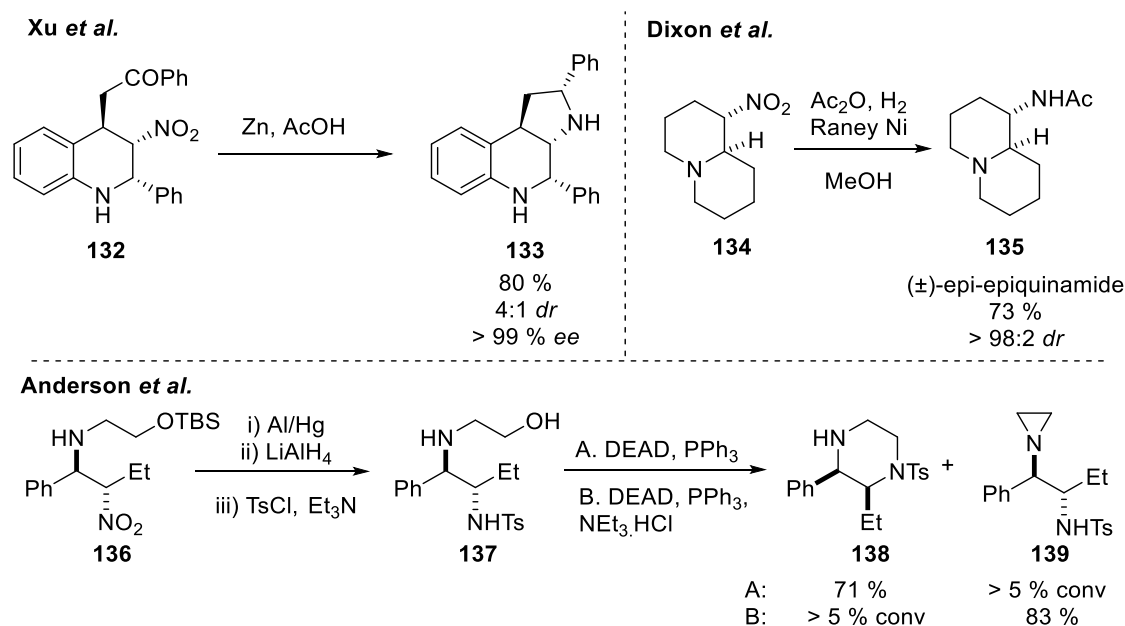
**Scheme 38.** Reduction of a  $\beta$ -nitroacetamide with aluminium amalgam

Hydrogenation with Pd/C was then carried out affording 1,2-diamines **131** in good to excellent yields. Where PG = allyl, or another group labile to hydrogenation the hydroxylamine can be reduced to the 1,2-diamine using LiAlH<sub>4</sub>.

#### 1.2.2.2 Formation of 1,2-diamino heterocycles

In many cases, formation of 1,2-diamines is followed by their incorporation into nitrogen-containing heterocycles. Nitro-Mannich reaction followed by reduction has led to the synthesis of various 1,2-diamine-containing heterocycles and natural products. These include the formation of tetrahydroquinolines and indolines (**Schemes 26 & 32**)<sup>60, 65</sup> piperidines,<sup>88a, 89</sup> (**Scheme 128**) pyrrolidines,<sup>58, 90</sup> piperazines,<sup>82c, 91</sup> their derivatives and other ring systems.

Various examples of heterocycles containing 1,2-diamines from reduction of the nitro-Mannich product  $\beta$ -nitroamines are shown in **Scheme 39**. Reduction of tetrahydroquinoline **132** using Zn/AcOH by Xu<sup>92</sup> results in generation of a primary amine, followed by an *in situ* reductive amination affording the tricyclic core structure **133**. Reduction of the  $\beta$ -nitroamine bicycle **134** using Raney nickel followed by acetylation by Dixon results in the formation of the alkaloid ( $\pm$ )-*epi-epi*-epiquinamide **135**.<sup>89b</sup>



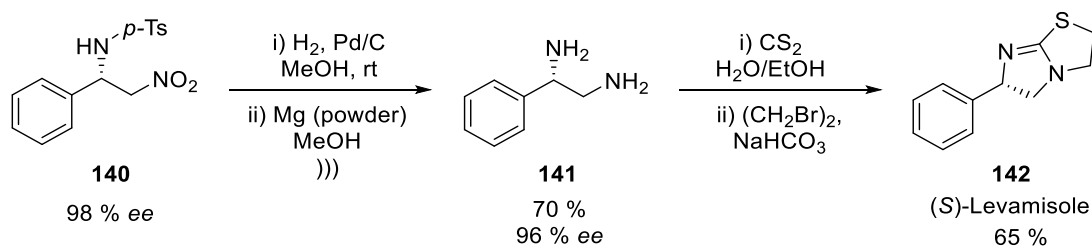
**Scheme 39.** Formation of 1,2-diamine containing heterocycles via various reduction reactions of  $\beta$ -nitroamines

Synthesis of piperazines **138** or aziridines **139** was carried out by Anderson *et al.* (**Scheme 39**). Reduction by aluminium amalgam followed by  $\text{LiAlH}_4$  (as previously described: **Scheme 38**) followed by tosylation of the primary amine results in the formation of protected 1,2-diamine **137**. Conducting an intramolecular cyclisation of **137** with DEAD/ $\text{PPh}_3$  (conditions A) results in the formation of a six-membered piperazine ring as the major product (> 95:5 conversion **138:139**). The addition of  $\text{NEt}_3\cdot\text{HCl}$  to the reaction mixture results in a switch in cyclisation mode and formation of aziridine **139** (> 95:5 conversion). Six-membered ring formation is thought to occur when NHTs is deprotonated by the DEAD anion and undergoes Mitsunobu cyclisation. When the weak acid  $\text{NEt}_3\cdot\text{HCl}$  is present, it is thought to protonate the DEAD anion. Without formation of the NTs anion, ring closure of the more basic alkyl amine takes place, forming the three-membered ring.

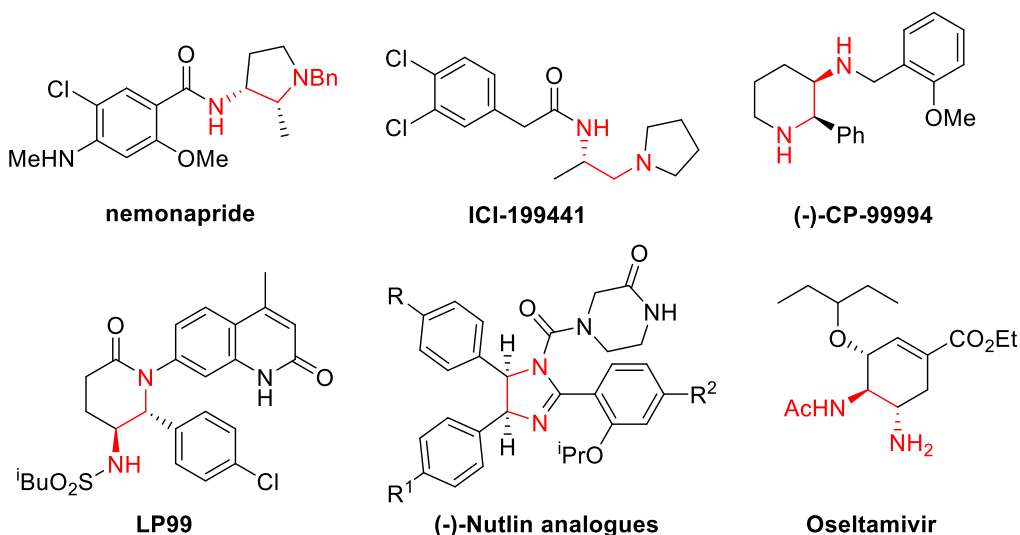
### 1.2.2.3 Applications in synthesis

The ubiquitous presence of the amine functionality in natural products and biologically active molecules makes them attractive targets for synthesis using the nitro-Mannich reaction. An example of synthesis of a vicinal di-nitrogen compound via reduction of  $\beta$ -nitroamines is the synthesis of (*S*)-Levamisole by Kureshy (**Scheme 40**).<sup>93</sup> Hydrogenation followed by deprotection of  $\beta$ -nitroamine **140** uncovers 1,2-diamine **141** with negligible loss of *ee*. A double cyclisation was then performed to give the drug (*S*)-Levamisole **142**.

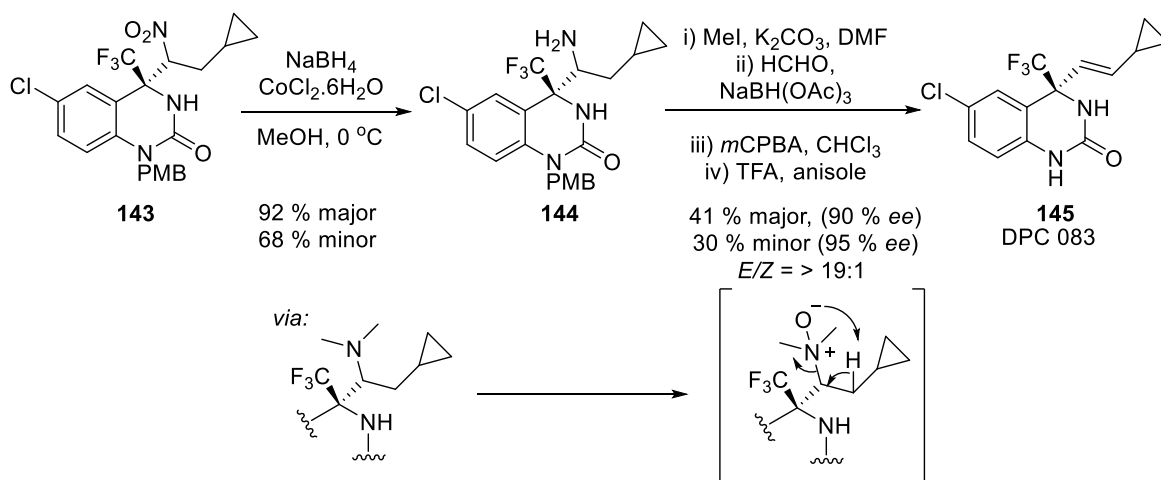


**Scheme 40.** Synthesis of (S)-Levamisole

Other syntheses resulting from nitro-Mannich reaction and reduction include the synthesis of clinically relevant molecules (+)-CP-99994, ICI-199441 and nemonapride by Shibasaki,<sup>31, 90</sup> synthesis of (-)-CP-99994 by Takemoto,<sup>38</sup> synthesis of LP99 by Dixon,<sup>89c</sup> synthesis of Oseltamivir by Lu,<sup>17c</sup> (-)-Nutlin-3 ( $R = R^1 = \text{Cl}$ ,  $R^2 = \text{OMe}$ ) and its analogues by Johnston<sup>87b, 94</sup> (**Scheme 41**).

**Scheme 41.** Synthesis of biologically active molecules synthesised from 1,2-diamines generated via the nitro-Mannich reaction

Synthesis of anti-HIV drug candidate DPC 083 **145** (**Scheme 42**) via reduction of nitro-Mannich product **143** was reported by W. Wang in 2011.<sup>95</sup> Two diastereomers (unassigned) are created by the nitro-Mannich reaction, and simultaneous syntheses of **145** is shown using the separated diastereomers.



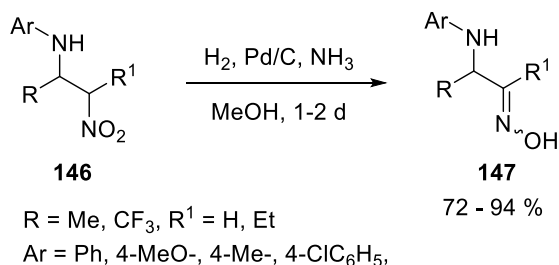
Scheme 42. Synthesis of DPC 083 by W. Wang

Alkylation of the primary amine **144** followed by formation of an *N*-oxide and subsequent cope elimination leads to the *N*-PMB protected target with a good *E/Z* ratio of > 19:1. Deprotection affords DPC 083 **145** in 41 % yield (major isomer) and 30 % yield (minor isomer) both in high enantiomeric excess.

### 1.2.3 Other transformations of the nitro group

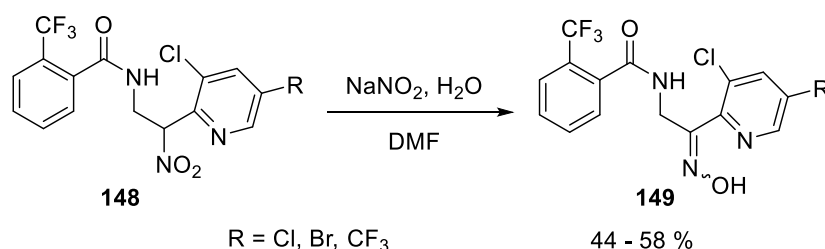
#### 1.2.3.1 Conversion to oximes

Few examples of the transformation of  $\beta$ -nitroamines to their oxime derivatives have been reported. Use of aluminium amalgam by Garcia and Cid gave an oxime as a by-product (8 %) in the reduction of a  $\beta$ -nitroamine.<sup>17b</sup> A recent report by Vovk and Nenajdenko details reduction to  $\alpha$ -aminooximes of a range of  $\beta$ -nitroamines generated via the nitro-Mannich reaction (Scheme 43).<sup>96</sup> Very good to excellent yields are achieved using  $\text{H}_2$ , Pd/C and sat aq. ammonia solution. No comment is given as to the orientation of the oxime (*E/Z*).



Scheme 43. Reduction of a nitro group to an oxime via hydrogenation

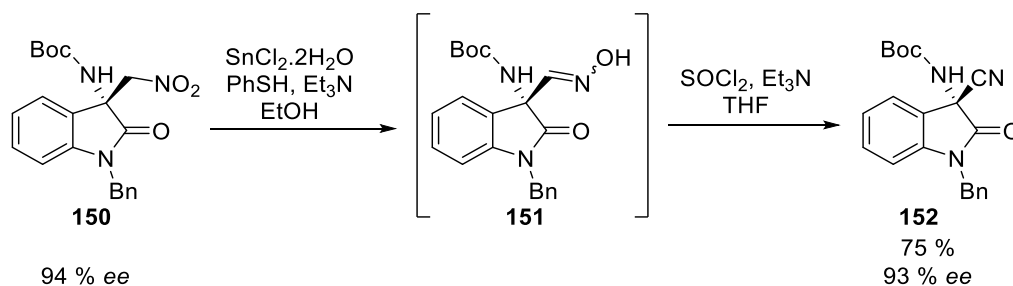
A further example details nitro reduction to oxime **149** using sodium nitrite in water and DMF, however only three examples are given, in moderate to good yields (**Scheme 44**). The *E:Z* ratio is not given.<sup>97</sup>



**Scheme 44.** Reduction of a nitro group to an oxime using sodium nitrite

### 1.2.3.2 Conversion to nitriles

Only one example of conversion of a  $\beta$ -nitroamine to an  $\alpha$ -aminonitrile exists, despite their potential use in further synthetic transformations.<sup>98</sup> Conversion of *N*-Boc protected Isatin-derived  $\beta$ -nitroamine **150** to the corresponding  $\alpha$ -aminonitrile **152** was carried out using SnCl<sub>2</sub>·2H<sub>2</sub>O/PhSH/Et<sub>3</sub>N followed by addition of SOCl<sub>2</sub>/Et<sub>3</sub>N. The reaction proceeds via initial formation of the aldoxime **151** followed by *in situ* dehydration of the oxime to form the nitrile **152** in good yield and with negligible loss of *ee*.

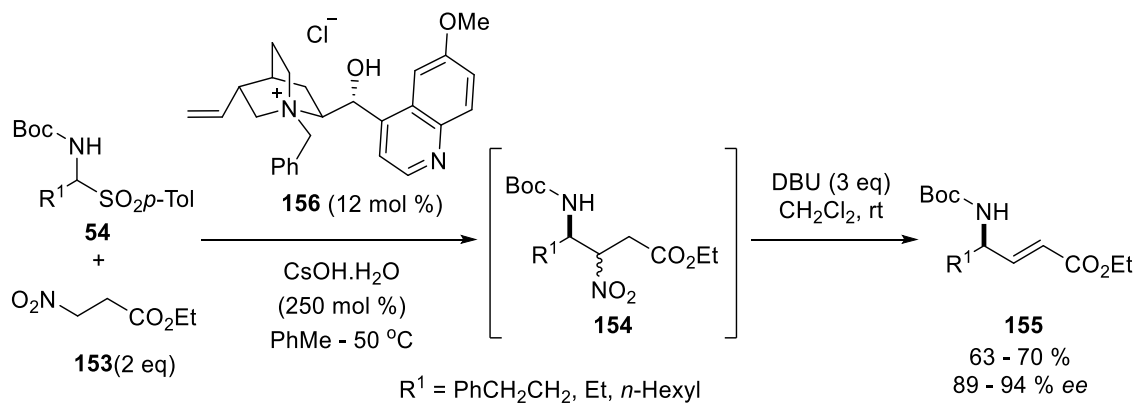


**Scheme 45.** Conversion of a  $\beta$ -nitroamide to an  $\alpha$ -aminonitrile

### 1.2.3.3 Elimination of the nitro group to form alkenes

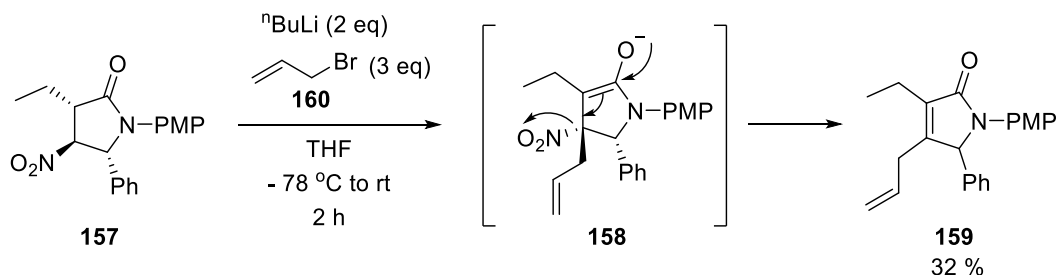
The removal of the nitro group from a  $\beta$ -nitroamine to give an alkene may be conducted via the elimination of nitrous acid (HNO<sub>2</sub>).<sup>49a, 76</sup> Desired base-catalysed elimination of nitrous acid can be problematic due to the acidity of the nitro group, leading to nitronate formation. However in the presence of a vicinal acidic proton, or in the case of the enhanced stability of an alkene, elimination of nitrous acid may be preferable via an E<sub>1cb</sub> mechanism. Elimination is usually carried out by deprotonation but may also occur as an unwanted side-reaction.<sup>61, 76a</sup> Palomo details the elimination of nitrous acid from *N*-Boc

protected  $\beta$ -nitroamines **154** following the nitro-Mannich reaction. This affords vinylogous amino acids **155** in good yields and excellent *ee* over two steps (**Scheme 46**).<sup>43c</sup>



**Scheme 46.** Elimination of nitrous acid to give an alkene

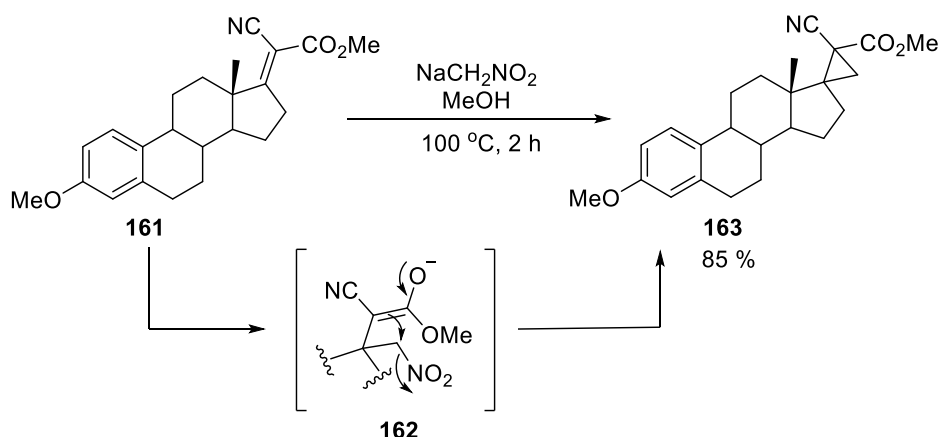
Another example of an addition-elimination follows an attempted allylation of the nitro group of pyrrolidine-2-one **157** (**Scheme 47**). Deprotonation with  $n\text{BuLi}$  led to the formation of stabilised anion **158**, followed by elimination of  $\text{NO}_2$  with the formation of unsaturated pyrrolidine-2-one **159** in moderate yield.<sup>58</sup>



**Scheme 47.** Addition-elimination reaction resulting in elimination of the nitro group

#### 1.2.3.4 Substitution reactions

Substitution of the nitro group may be performed via ionic<sup>75a</sup> or radical<sup>75b</sup> methods.<sup>49a</sup> The nitro group is known to act as a leaving group for ionic substitution in the presence of a Lewis acid,<sup>99</sup> palladium(0) catalyst (for allylic nitro groups),<sup>100</sup> or in certain cases of cyclopropanation with electron-deficient alkenes.<sup>101</sup> An example of an ionic nucleophilic substitution of a nitro group is the cyclopropanation of a steroid enone (**Scheme 48**).<sup>101a</sup> Michael addition of the sodium salt of nitromethane to enone **161** gave adduct **162**. Nucleophilic attack ( $\text{S}_{\text{N}}2$ ) of the enolate on the nitromethylene then eliminates  $\text{NO}_2$  to afford 1,1,2,2-tetrasubstituted cyclopropane **163**.



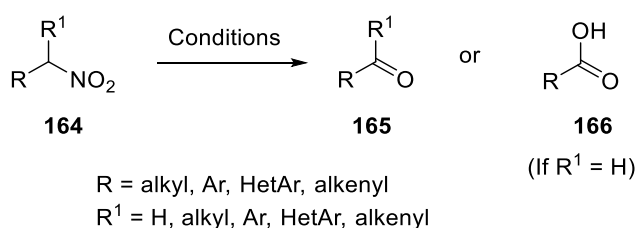
**Scheme 48.** Intramolecular substitution of a nitromethylene adduct

Radical substitution or elimination of the nitro group is also possible, however this will be discussed in section 1.4.

### 1.3 The Nef reaction

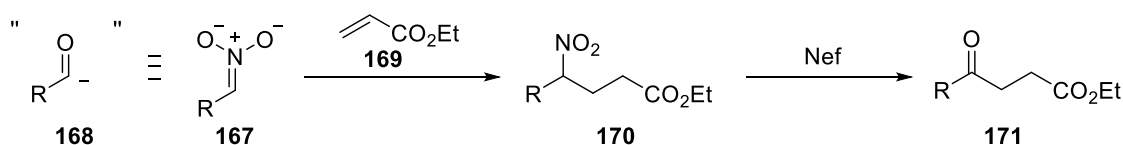
#### 1.3.1 Overview

The Nef reaction<sup>71, 102</sup> was first observed in the late 19<sup>th</sup> century, and today represents a wide array of methods for the conversion of a primary or secondary nitro group to a carbonyl (**Scheme 49**). Primary nitro groups may be converted to aldehydes or carboxylic acids depending on the reagents used and secondary nitro groups are converted to ketones. In this way the nitro group to carbonyl conversion may be seen as similar to the oxidation of primary and secondary alcohols.<sup>71b</sup>



**Scheme 49.** The Nef reaction

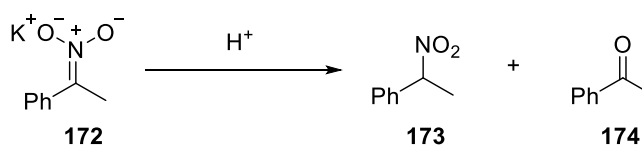
The ability to transform the nitro group directly to a carbonyl increases the utility of the nitro group in synthesis. The nitro group acts as an acyl anion equivalent **168** that may be uncovered after reaction of the nitro compound has taken place. Certain carbonyl containing molecules can be difficult to make via other methods, for example 1,4-dicarbonyls **171**. These can be furnished simply via Michael addition of a nitroalkane to an acrylate **169**, followed by Nef reaction (**Scheme 50**).



**Scheme 50.** Formation of a 1,4-dicarbonyl via the Nef reaction

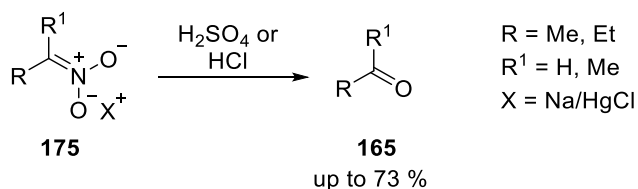
### 1.3.2 Initial discovery

The first nitro to carbonyl conversion was observed in 1893 by Konovalov.<sup>103</sup> Hydrolysis of the potassium salt of 1-phenylnitroethane **172** with dilute acetic, nitric or sulfuric acid (or via passing CO<sub>2</sub> through an alcoholic solution) resulted in a mixture of 1-phenylnitroethane **173** and acetophenone **174**, yields unknown (**Scheme 51**).



**Scheme 51.** The first reported conversion of a nitro group to a carbonyl

This was followed by an independent, more comprehensive report by Nef<sup>104</sup> the following year detailing the hydrolysis of sodium (or mercuric chloride) salts of nitromethane, nitroethane and nitropropane. Hydrolysis with cold, dilute sulfuric or hydrochloric acid led to the formation of formaldehyde, acetaldehyde and acetone respectively in up to 73 % yield (**Scheme 52**).



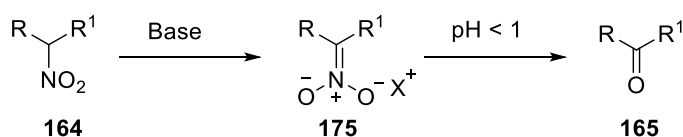
**Scheme 52.** Nitronate to carbonyl conversion by Nef

This reaction constitutes the definition of the original Nef reaction: ‘The acid hydrolysis of a salt of a primary or secondary nitroalkane to yield an aldehyde or ketone, respectively, and nitrous oxide.’<sup>102a</sup> However, the passing of over a century has seen many advances in the methods available for this transformation. The Nef reaction can now be divided into three types in which the majority of methods lie, with some exceptions. These groups include a) solvolytic (acid hydrolysis of a nitronate), b) oxidative (oxidation of a nitronate or nitronic acid) and c) reductive (direct reduction of the nitro group or reduction of the nitronate) Nef reactions. Comprehensive reviews<sup>71, 102</sup> detail many examples of each, hence a short review of important and interesting literature will be given here, with

applications to  $\beta$ -nitroamines and use of the Nef reaction in synthesis. Only the Nef reaction of saturated nitroalkanes will be discussed; direct Nef reduction of nitroalkenes or nitronate anions generated via reduction of nitroalkenes has been reviewed<sup>71</sup> and is less applicable to this work.

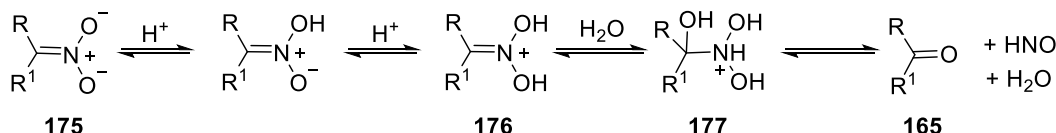
### 1.3.3 Solvolysis (Acid hydrolysis of nitronates)

Solvolysis is the original reaction conditions described by Nef, hydrolysis of a nitronate salt using acid (**Scheme 53**). The harsh reaction conditions required exclude base or acid sensitive molecules from this method.



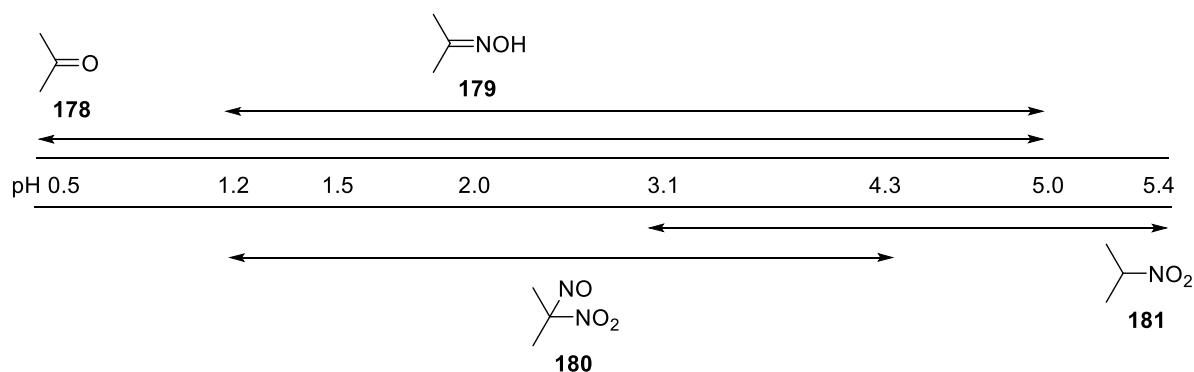
**Scheme 53.** Solvolytic Nef reaction

A variety of base/acid combinations have been described, however solvolysis proceeds via a common mechanism. Addition of nitronate **175** to acid at pH <1 results in the formation of protonated nitronic acid **176**. Attack of water on the C=N bond gives intermediate **177**, which on decomposition gives the product carbonyl **165**, water and HNO (hyponitrous acid)(**Scheme 54**).



**Scheme 54.** Mechanism of hydrolysis of a nitronate, leading to carbonyl formation

It is important that the pH of the solution is very low (pH < 1) in order to avoid side reactions during hydrolysis of the nitronate. Formation of undesired by-products is related to acidity of the reaction; by-product distribution upon acidification of the nitronate of 2-nitropropane is shown against a pH gradient from 0.5 to 5.4 (placement on the molecules on the scale is at highest percentage yield - **Fig. 4**). Interestingly, oximes **179** and pseudonitroles **180** ( $\alpha$ -nitroso-nitro compounds) are present across a wide pH range, (1.2 – 5 and 1.2 – 4.3 respectively) with protonation of the nitronate occurring at higher pH only (3.1 – 5.4) and exclusively at high pH (5.4). Optimum conditions for protonation of the nitronate at oxygen is at pH < 1.2, as at pH 1.2, 20 % of material is lost to side reactions.<sup>105</sup>

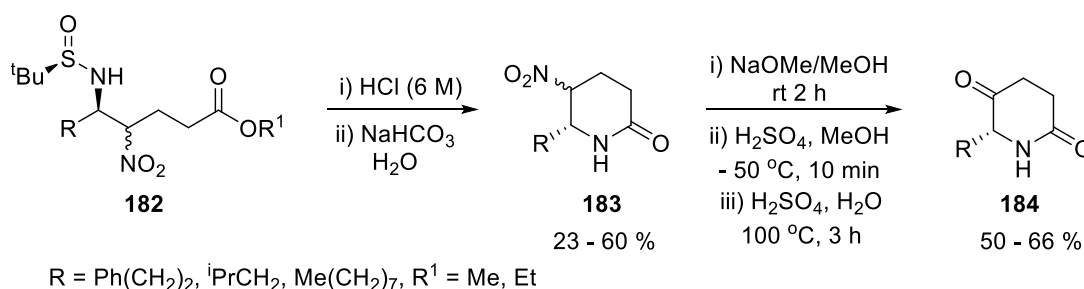


**Fig. 4.** Nef reaction product distribution depending on pH

To avoid the formation of these undesired by-products, the nitronate is usually added to the acid as this results in rapid di-protonation of the nitronate as it encounters a large excess of acid. Formation of  $\alpha$ -nitrosone compounds may occur in the presence of nitrous acid ( $\text{HNO}_2$  produces the nitrosating agent  $\text{NO}^+$ ), however this can be avoided by the addition of urea.<sup>106</sup>

### 1.3.3.1 Solvolytic Nef reaction of $\beta$ -nitroamines

The first solvolytic Nef conversion of a  $\beta$ -nitroamine was performed by Yus<sup>17d</sup> in 2015 using  $\text{NaOMe}/\text{H}_2\text{SO}_4$  (**Scheme 55**). The reaction was carried out on a piperidin-2-one derivative generated by initial nitro-Mannich reaction followed by deprotection-lactamisation. Nef reaction of piperidin-2-ones **183** followed by additional hydrolysis of an acetal generated *in situ* from the methanolic solvent afforded piperidin-2,5-diones **184** in good yields.



**Scheme 55.** Solvolytic Nef reaction of 5-nitropiperidine-2-ones

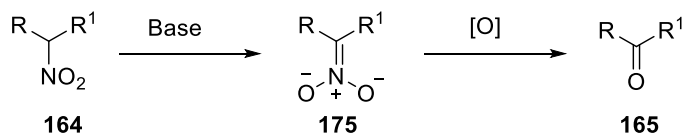
Interestingly, the Nef reaction was carried out on the deprotected lactam **183** and not the nitro-Mannich product **182**. The highly acidic conditions of the Nef reaction would likely deprotect the acid-labile  $t$ -Butylsulfonylamine. This would lead to the generation of a primary amine vicinal to a carbonyl group, and problems with self-condensation and epimerisation may arise under the acidic conditions. Many nitro-Mannich reactions use



acid-labile protecting groups (especially *N*-Boc imines)<sup>4</sup> and this may be why protected  $\beta$ -nitroamines are rarely subjected to the Solvolytic Nef reaction.

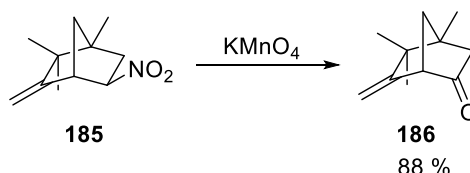
### 1.3.4 Oxidative Nef reaction

The oxidative Nef reaction consists of deprotonation adjacent to the nitro group generating a nitronate followed by C=N bond cleavage by an oxidant, generating a C=O bond (**Scheme 56**).



**Scheme 56.** Oxidative Nef reaction

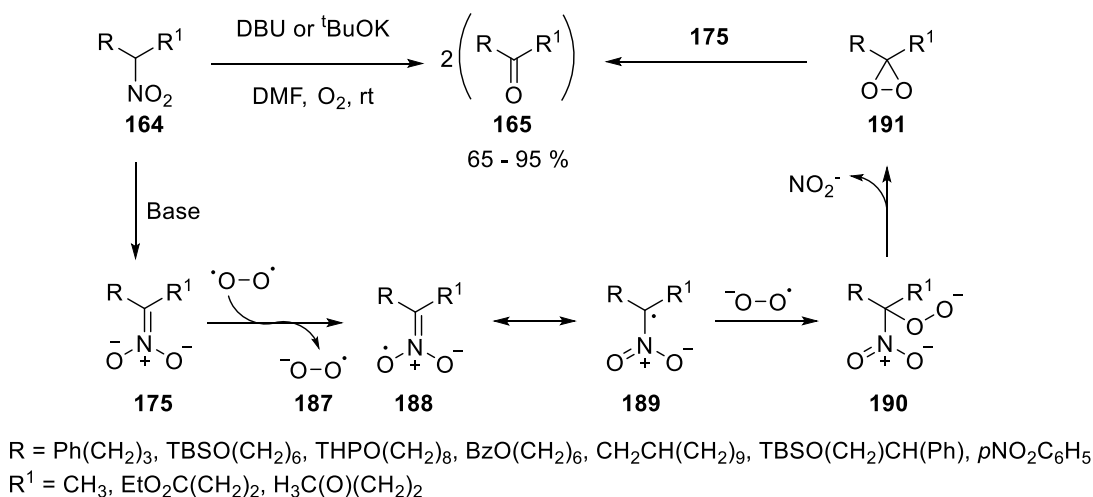
The first oxidative Nef reactions were discovered in the early 20<sup>th</sup> century.<sup>102b</sup> The use of potassium permanganate<sup>107</sup> was found to be an effective replacement for acid hydrolysis of the nitronate, resulting in higher yields in many cases. Interestingly it was also found that the C=N bond is cleaved faster than the C=C bond of alkenes, hence selective Nef reactions could be performed on unsaturated molecules (**Scheme 57**).<sup>108</sup> Nef reaction of 4-methyl-6-nitrocamphene **185** under oxidative conditions results in smooth conversion to the carbonyl **186** without cleavage of the alkene.



**Scheme 57.** Oxidative Nef reaction

Both primary and secondary nitroalkanes may be oxidised to aldehydes and ketones respectively, however addition of excess permanganate results in full oxidation of primary nitroalkanes to the carboxylic acid.<sup>109</sup> The oxidant required for a process may be judged on sensitivity of functional groups present in the molecule to the reagent; different reagents or conditions are used for primary nitro groups depending on whether full or partial oxidation is required. Additional oxidants used include Oxone®,<sup>110</sup> Ozone,<sup>111</sup> O<sub>2</sub>,<sup>112</sup> H<sub>2</sub>O<sub>2</sub>,<sup>113</sup> DMDO<sup>114</sup> and many others.<sup>71, 102</sup> These all proceed via cleavage of the C=N bond, however a range of mechanisms exist; both ionic and radical.

Hayashi detailed the interesting reaction of a nitronate with molecular oxygen and significant mechanistic investigation.<sup>112d</sup> Reaction is thought to proceed via SET from the nitronate to the peroxy radical, generating superoxide anion **187** which combines with the  $\alpha$ -nitro radical **189** to give intermediate **190**. Loss of the nitrite anion leads to the formation of a dioxirane **191** which is a strong oxidising agent itself, and is able to oxidise the initial nitronate anion **175** to a carbonyl **165** (**Scheme 58**). This is supported by molecular labelling ( $^{18}\text{O}$  incorporation from  $^{18}\text{O}_2$  gas used, no incorporation from  $\text{N}^{18}\text{O}_2$  or  $^{18}\text{OH}_2$ ), radical clock experiments and incorporation of a sulfur tether which undergoes intramolecular oxidation by the dioxirane **191** to a sulfoxide. The reaction is promoted by several bases however the highest yields are observed using DBU or  $t\text{BuOK}$  in DMF under  $\text{O}_2$ .<sup>112d</sup>

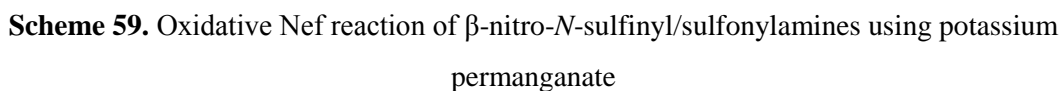


**Scheme 58.** Oxidative Nef reaction of nitronate anions with molecular oxygen

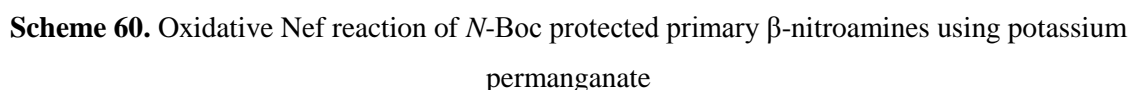
#### 1.3.4.1 Oxidative Nef reactions of $\beta$ -nitroamines

Conversion of protected  $\beta$ -nitroamines to their  $\alpha$ -aminocarbonyl derivatives has been performed using potassium permanganate on primary<sup>15-16, 115</sup> or secondary<sup>17b, 116</sup> nitro groups to give carboxylic acids or ketones respectively.

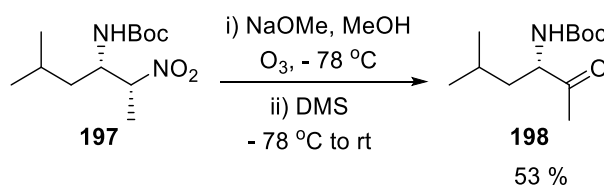
Both Garcia<sup>17b</sup> and Yus<sup>116</sup> performed oxidative Nef reactions of secondary  $\beta$ -nitroamine derivatives **192** and **194** using potassium permanganate (**Scheme 59**). Only moderate yields were achieved using Yus' protocol. Garcia found that *N*-sulfinyl derivatives did not undergo Nef reaction hence oxidation of the *N*-sulfinyl protecting group to *N*-sulfonyl was performed using mCPBA. Oxidative Nef reaction of the *N*-sulfonyl protected  $\beta$ -nitroamines **192** then proceeded in high yields. Some epimerisation of the stereocentre



Oxidation of primary nitro  $\beta$ -nitroamine derivatives is extremely useful as this leads to the generation of an amino acid framework. A report by Petrini detailed Nitro-Mannich reaction using chiral auxiliaries leading to the formation of *N*-Boc protected  $\beta$ -nitroamines **23** (**Scheme 7**). Oxidative Nef reaction using potassium permanganate generated carboxylic acids which were methylated to provide amino acid methyl esters **196** in high yields (**Scheme 60**).<sup>16</sup> A later report by the same author details the formation of a dipeptide via nitro-Mannich reaction of a chiral  $\alpha$ -amidosulfone with ‘acyl anion equivalent’ nitromethane. Nef reaction using the same conditions liberates the carboxylic acid.<sup>115</sup>



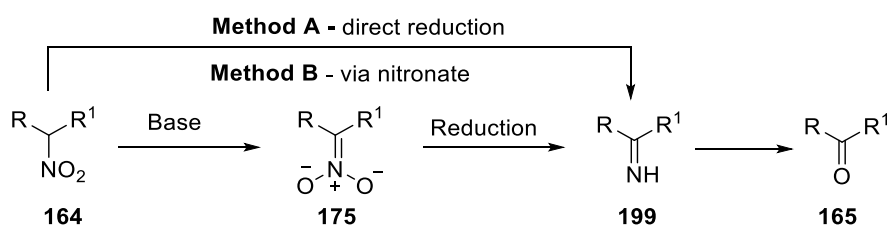
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**Scheme 61.** Oxidative Nef reaction of *N*-Boc protected  $\beta$ -nitroamines using ozone

### 1.3.5 Reductive Nef reaction

The reductive Nef reaction is the reduction of the nitro compound to an imine **199**, which can then undergo hydrolysis to the desired carbonyl compound **165** (**Scheme 62**). In contrast to the aforementioned solvolytic/oxidative Nef reactions, direct reduction of the nitro compound is possible without the need for nitronate formation (**Method A**). This method facilitates the Nef reaction in the presence of base-sensitive functional groups. Alternatively, reduction via a nitronate is also possible (**Method B**).



**Scheme 62.** The reductive Nef reaction

#### 1.3.5.1 Reductive Nef using low-valent metal species

Many reagents for the reductive Nef reaction are available, including low valent transition metal reducing agents titanium (III) chloride,<sup>118</sup> vanadium (II) chloride<sup>119</sup> and chromium (II) chloride.<sup>120</sup> The most commonly applied of these is the McMurry method, reduction of a nitro group or nitronate to a carbonyl using titanium (III) chloride. The reaction is thought to proceed via a series of single-electron transfer (SET) steps to give common oxime intermediate **202**. Variation of the reaction conditions can lead to the isolation of the oxime or further reduction to an imine **199** which upon hydrolysis affords carbonyl **165** (**Scheme 63**).<sup>118b</sup>

[illegible]

**Scheme 64.** Reductive Nef reaction via the McMurry protocols

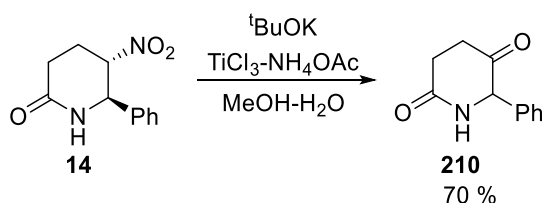
### Other reductive Nef reactions

Less commonly used reductive Nef methods include tributylphosphine/diphenyl disulphide,<sup>72d, 121</sup> tin (II) chloride<sup>122</sup> and iron powder in acid.<sup>123</sup>

#### 1.3.5.2 Reductive Nef reactions of $\beta$ -nitroamines

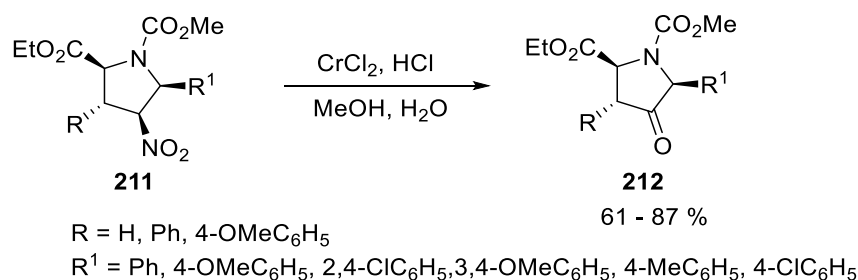
In comparison to the oxidative Nef reaction, relatively few examples of the reductive Nef reaction of  $\beta$ -nitroamines and their derivatives are known and are exclusive to the use of  $\text{TiCl}_3$ <sup>124</sup> or  $\text{CrCl}_2$ <sup>120c</sup> reducing agents. However, these examples contribute to the synthesis of heterocycles or biologically relevant molecules and clearly show the potential of  $\beta$ -nitroamines.

A report by Iwabuchi<sup>124b</sup> detailed the Nef reaction of 5-nitropiperidin-2-one **14** originally constructed via the nitro-Mannich reaction (**Scheme 5**).<sup>13</sup> The reaction proceeded via formation of the potassium nitronate, followed by reduction using  $\text{TiCl}_3\text{-NH}_4\text{OAc}$  to afford piperidine-2,5-dione **210** in good yield (**Scheme 65**).



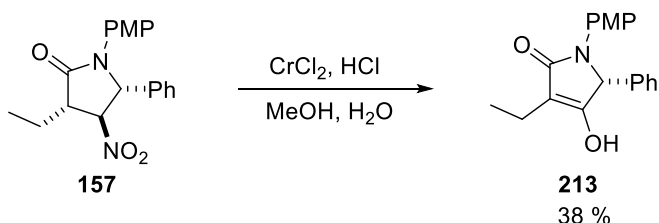
**Scheme 65.** Reductive Nef reaction using the McMurry protocol

A report by Nyerges<sup>120c</sup> details the use of  $\text{CrCl}_2$ , freshly prepared via zinc reduction of potassium dichromate in hydrochloric acid, for the reductive Nef reaction of 3-nitropyrrolidines **211** to the corresponding pyrrolidin-3-ones **212** in good to excellent yields (**Scheme 65**). Previous attempts at the Nef reaction of the *N*-H derivatives of pyrrolidines **211** via several methods were unsuccessful, leading to the formation of pyrroles.<sup>125</sup> The reduction of nitro groups by chromium (II) chloride is thought to proceed via a similar mechanism to the direct titanium (III) reduction (Method A, **Scheme 63**).<sup>120b</sup>



**Scheme 66.** Reductive Nef reaction of 3-nitropyrrolidines using chromium (II) chloride

A report by Anderson detailed the chromium (II) chloride mediated Nef reaction of pyrrolidine-2-one **157** to afford pyrrolone **213** in moderate yield. Reaction using the McMurry method showed no conversion under various conditions.<sup>58</sup>

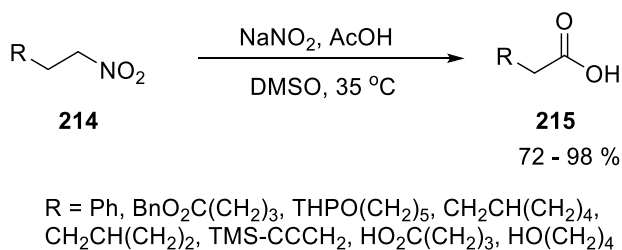


**Scheme 67.** Reductive Nef reaction of pyrrolidin-2-ones using chromium (II) chloride

### 1.3.6 Nef reactions via other methods

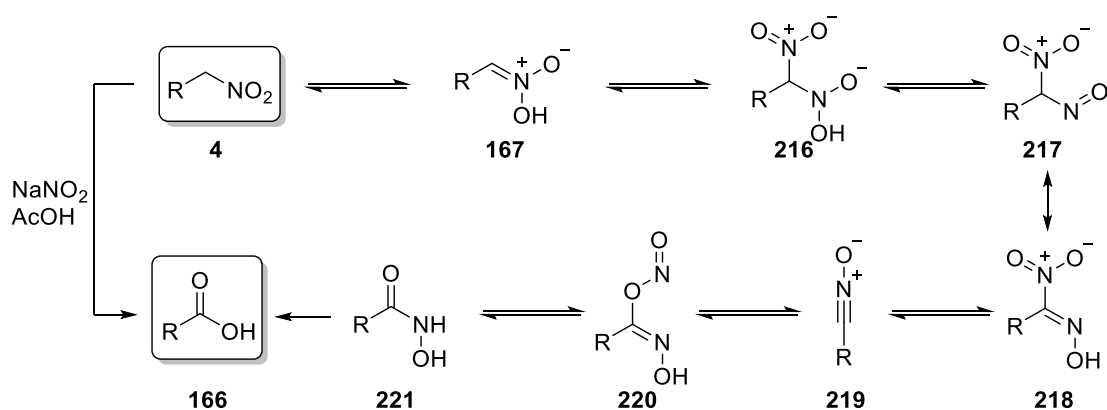
In addition to the main solvolytic, oxidative and reductive methods, a plethora of alternative methods for the nitro to carbonyl conversion exist.<sup>71, 102</sup> These include biocatalysis,<sup>126</sup> use of KH/TMS-Cl,<sup>127</sup> sodium nitrite,<sup>128</sup> DBU<sup>129</sup> and NIS/H<sub>2</sub>O/K<sub>2</sub>CO<sub>3</sub>.<sup>130</sup>

Nef reactions for the mild conversion of nitro groups in the presence of sensitive functional groups are incredibly important in the synthesis of large multi-functional molecules. The discovery of the sodium nitrite/alkyl nitrite Nef reaction in the mid-20<sup>th</sup> century by Kornblum provided a general solution for the formation of both ketones and carboxylic acids, from secondary/primary nitro compounds respectively.<sup>131</sup> A study by Mioskowski<sup>128a</sup> of the reaction of sodium nitrite in the absence of alkyl nitrites led to the discovery of an improved method for the conversion of primary nitro compounds **214** in the presence of NaNO<sub>2</sub>/AcOH. The carboxylic acids **215** were formed in good to excellent yields with tolerance for a range of functional groups (**Scheme 68**).



**Scheme 68.** Nef conversion of a primary nitro compound to a carboxylic acid using sodium nitrite and acetic acid

The mechanism is thought to proceed via initial formation of a nitronic acid, followed by *N*-attack of the nitrite ion to give intermediate **216**. Loss of water followed by tautomerisation affords nitrolic acid **218**, elimination of the nitrite anion generates a nitrile oxide **219** which undergoes *O*-attack by the nitrite anion to give nitrosated oxime derivate **220**. Loss of  $\text{NO}^+$  leads to hydroxamic acid **221** which is hydrolysed to give the carboxylic acid **166**. The nitrolic acid **218** can be isolated at lower reaction temperatures and even purified by column chromatography, addition of an alkene trap into the reaction leads to a 1,3-dipolar cycloaddition product, confirming a nitrile oxide intermediate in the mechanism.<sup>128a</sup> A nitrosonium ion ( $\text{NO}^+$ ) is thought to be generated under the reaction conditions as a nitrosating reagent (**Scheme 69**).

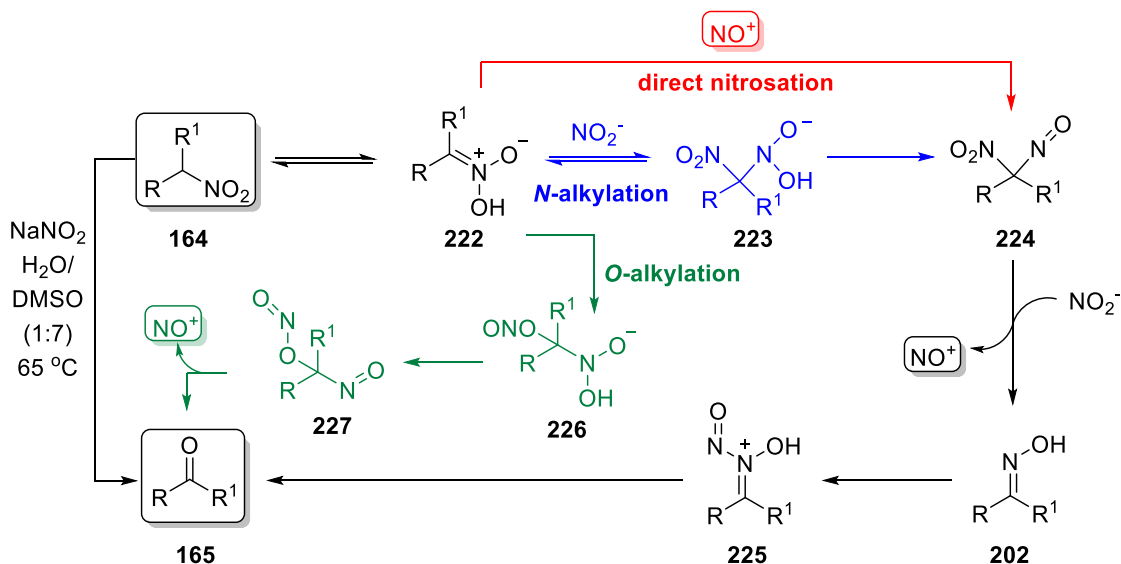


**Scheme 69.** Postulated mechanism for the Nef reaction of primary nitro compounds using sodium nitrite in acetic acid

An improved method for the conversion of secondary nitro compounds to their corresponding ketones was later reported by Mioskowski.<sup>128b</sup> In this case, the reaction is performed using  $\text{NaNO}_2$  in the presence of water, acetic acid is not required. The reaction is thought to be auto-catalytic, generating the required nitrosating species  $\text{NO}^+$  during the course of the reaction. A variety of mechanisms have been postulated for this



transformation (**Scheme 70**), including both *N*- or *O*-attack of the nitrite anion on the nitronic acid **222**. In both cases, loss of  $\text{OH}^-$  leads to the formation of substituted nitroso compounds **224** or **227**. Loss of  $\text{NO}_2^-$  from **224** leads to oxime **202**. Cleavage of the ONO adduct **227** via a radical or ionic process releases 2 molecules of the nitrosating agent ( $\text{NO}^+$ ).



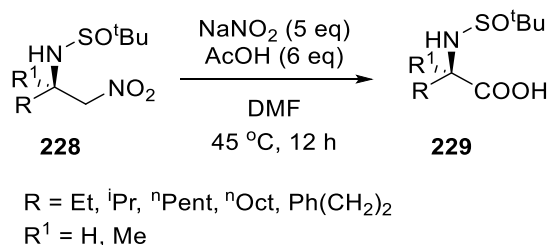
**Scheme 70.** Mechanism of Nef reaction of secondary nitro compounds using sodium nitrite

Release of  $\text{NO}^+$  (and other nitrogen oxide species) during the reaction leads to nitrosation of intermediate oxime **202**; direct nitrosation of nitronic acid **222** can also take place, giving a faster pathway to pseudonitrole **224**. The ratio of oxime to ketone formed in the reaction correlates with electron density on the nitrogen atom of the oxime. Nitrosation of electron rich oximes is more successful leading to a higher ketone to oxime ratio, hence the nature of the R groups are important. When the oxime is electron poor, nitrosation of the oxime is not efficient, and conversion to the ketone is low.

### 1.3.6.1 Nef reactions of $\beta$ -nitroamines using sodium nitrite

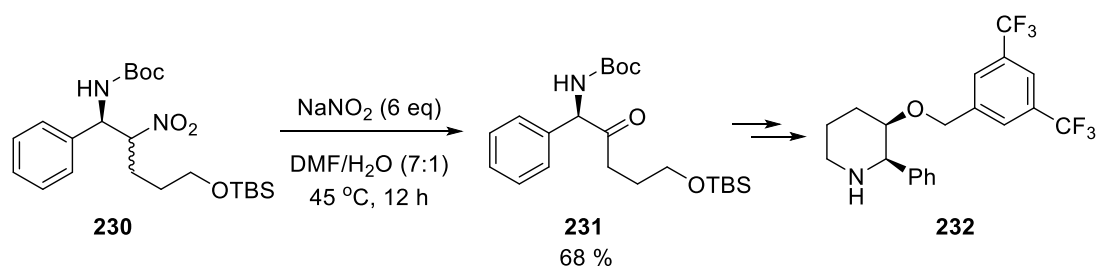
The use of mild methods such as the  $\text{NaNO}_2$  processes described above is incredibly important for the Nef reaction of unstable or sensitive molecules. Owing to the sensitivity of  $\beta$ -nitroamines and their derivatives, this is often used as the method of choice to convert primary nitro groups to carboxylic acids,<sup>27, 38, 43e, 116, 132</sup> and some secondary nitro groups to ketones.<sup>88a</sup>

A report by Yus<sup>116</sup> details the conversion of *N*-sulfinyl protected primary  $\beta$ -nitroamines **228** to amino acid derivatives **229** in moderate to good yields (**Scheme 71**). The mild reaction conditions led to retention of the <sup>t</sup>butylsulfinyl protecting group.



**Scheme 71.** Nef reaction of *N*-sulfinyl- $\beta$ -nitroamines using sodium nitrite/acetic acid

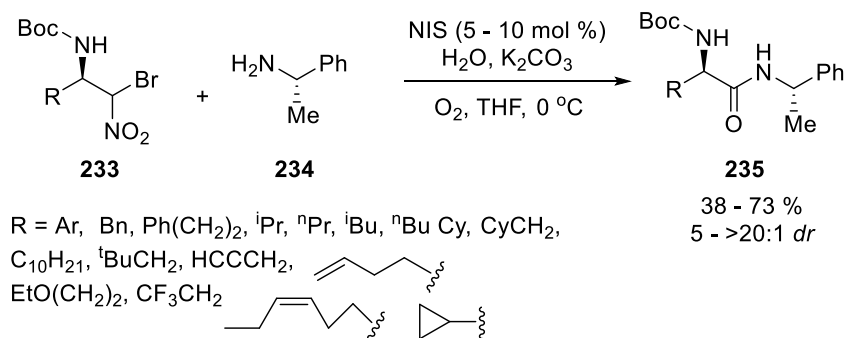
A Nef reaction of secondary *N*-Boc protected  $\beta$ -nitroamine **230** described by Kumaraswamy<sup>88a</sup> using sodium nitrite in DMF/H<sub>2</sub>O, afforded  $\alpha$ -amidocarbonyl **231** in good yield (**Scheme 72**). The *N*-Boc protecting group was retained due to the mild reaction conditions, which facilitated further functional group manipulations in the synthesis of biologically active target molecule L-(-)-733061 (**232**).



**Scheme 72.** Nef reaction of a secondary *N*-Boc protected  $\beta$ -nitroamine by sodium nitrite in the synthesis of L-(-)-733061

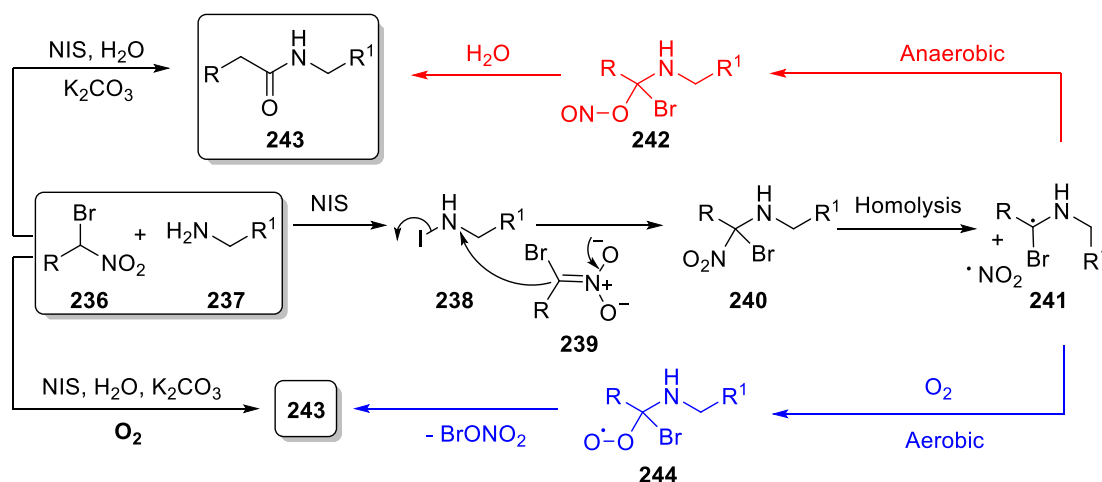
### 1.3.6.2 Synthesis of $\alpha$ -amidoamines via a Nef reaction-amide coupling

Applications of new methodology to the field of peptide synthesis has allowed the group of Johnston to make the synthesis of complex peptides and their derivatives less problematic by the use of umpolung acyl equivalent  $\alpha$ -bromonitroalkanes.<sup>130</sup> A range of  $\beta$ -bromo- $\beta$ -nitroamine derivatives **233**, synthesised via the organocatalytic nitro-Mannich reaction, were coupled with chiral amine **234** to form *N*-Boc  $\alpha$ -aminoamides **235** in moderate to good yields (**Scheme 73**).<sup>133</sup> Coupling of *N*-Boc protected  $\beta$ -bromo- $\beta$ -nitroamine **233** ( $\text{R} = 4\text{-ClC}_6\text{H}_5$ ) to a variety of enantiomerically pure amino acids also gave dipeptides.<sup>130</sup>



**Scheme 73.** Umpolung amide synthesis of *N*-Boc α-amidoamines by Johnston

The use of common protecting groups for peptide synthesis is tolerated (e.g. Fmoc, alloc).<sup>134</sup> The mechanism is thought to proceed via nucleophilic addition of the nitronate **239** to halo-amine **238**, generated via halogenation of amine **237** with an iodonium or bromonium ion. Tetrahedral intermediate **240** then requires a formal hydrolysis to generate the amide. It was found that this proceeds via two possible mechanisms (anaerobic or aerobic). Under anaerobic conditions, homolysis of the C-NO<sub>2</sub> bond results in formation of carbon radical **241** and a nitrite radical; these radicals can then recombine to give bromonitrite **242**. Water catalysed decomposition of the nitrite compound with extrusion of bromide generates amide **243**. Alternatively, under an oxygen atmosphere carbon radical **241** can trap O<sub>2</sub> to give peroxy radical **244**. This peroxy radical then decomposes eliminating BrONO<sub>2</sub>, forming amide **243** (**Scheme 74**).<sup>135</sup> The mechanistic hypothesis is supported by <sup>18</sup>O<sub>2</sub> labelling experiments. Incorporation of <sup>18</sup>O into the amide **243** from the nitro group (N<sup>18</sup>O<sub>2</sub>) under anaerobic conditions (no incorporation from H<sub>2</sub><sup>18</sup>O) suggests nitrite isomerisation (**Scheme 74**, anaerobic route). Incorporation of <sup>18</sup>O into the amide under <sup>18</sup>O<sub>2</sub> gas atmosphere suggests combination of O<sub>2</sub> with radical **241** (aerobic conditions).



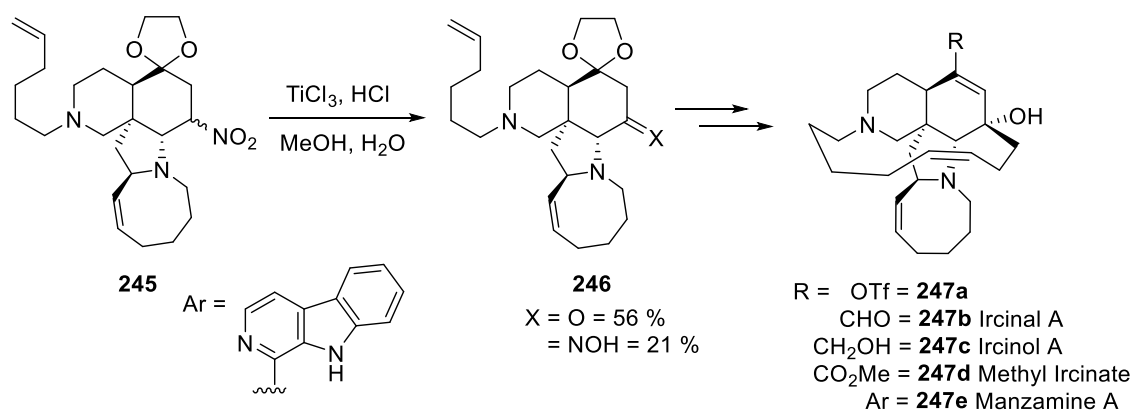
**Scheme 74.** Mechanism for umpolung amide synthesis

Initially stoichiometric amounts of NIS were used to iodinate the amine, however it was discovered that the bromonitroalkane can also act as a source of bromonium ion. Lower catalytic loading of NIS could be used in the presence of oxygen as a terminal oxidant, which is thought to regenerate electrophilic halogen sources (Br/I).<sup>133a</sup> Recent advances have seen one-pot amide formation from nitromethane-derived β-nitroamines via *in situ* bromination of the nitroalkane.<sup>136</sup> This would give the possibility of subsequent amide bond formation of primary β-nitroamine derivatives generated via the nitro-Mannich reaction, furthering its potential.

### 1.3.7 Synthetic applications of the Nef reaction of β-nitroamines

The carbon-carbon bond forming ability of the nitro group is well known, and the ability to transform the nitro group remains a powerful tool in the synthesis of highly complex molecules. A summary of some of the important uses of the Nef reaction on nitro-Mannich product β-nitroamines shows the importance of this reaction sequence and its potential application in total synthesis. In addition to the report detailed above (**Scheme 72**) by Kumaraswamy,<sup>88a</sup> synthesis of Manzamine A and related alkaloids by Dixon,<sup>124c</sup> synthesis of glycine transporter 1 inhibitors by Abbott GmbH & Co KG<sup>124a</sup> and peptide synthesis by Johnston<sup>130, 133-135</sup> are described.

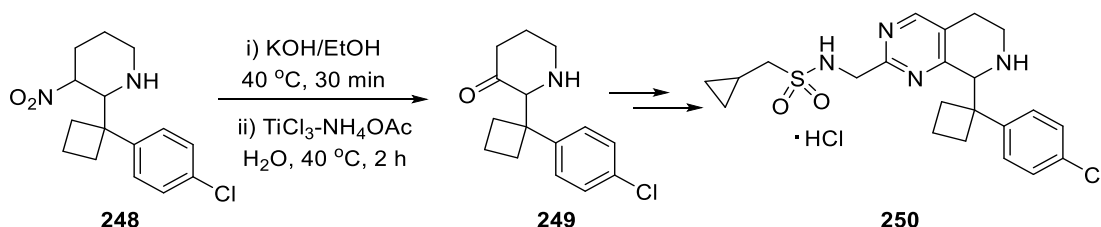
The synthesis of Manzamine A **247e** and alkaloids **247b** – **247d** proceeds via common intermediate **247a**. Nitro-Mannich reaction generated β-nitroamine **245**, which underwent reductive Nef reaction using the McMurry method (TiCl<sub>3</sub> at low pH) affording a mixture of ketone **246** and its oxime derivative (**Scheme 75**).



**Scheme 75.** Formation of marine natural products via the Nef reaction of a  $\beta$ -nitroamine

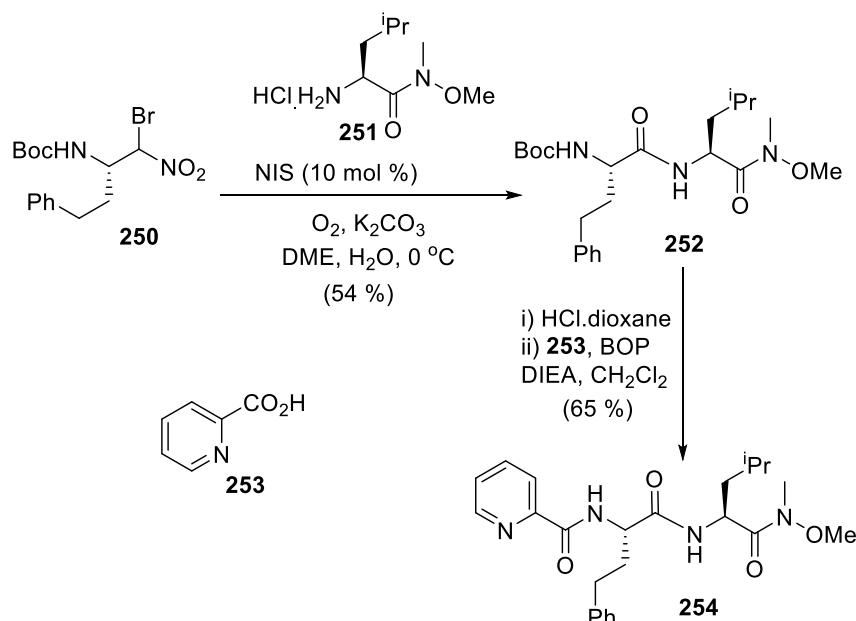
A range of methodologies were screened for the Nef reaction, however due to the sensitivity of the highly functional molecule, this proved the most reliable route. Further reaction of the ketone leads to the generation of intermediate **247a**, which is transformed into marine natural products Manzamine A, Ircinal A and Ircinol A.<sup>124c</sup>

Intermediate **249** is a central building block for a series of inhibitors of glycine transporter 1 (GlyT1) for example sulfonamide **250**.<sup>124a</sup> Initial nitro-Mannich reaction, lactamisation and reduction of the piperidin-2-one precursor furnishes 3-nitropiperidine **248**. Nef reaction of a secondary nitronate via the McMurry protocol (TiCl<sub>3</sub>-NH<sub>4</sub>OAc) generates ketone **249**. Purified yield is not given as the material is used directly in the next step.



**Scheme 76.** Nef reaction of a 3-nitropiperidine using the McMurry protocol and further use in the synthesis of glycine transporter 1 inhibitors (GlyT1)

The umpolung amide formation methodology described by Johnston was used for the synthesis of **254**, a peptide which is effective in reversing P-Glycoprotein-Mediated resistance to Carfilzomib.<sup>133b</sup> Coupling of  $\alpha$ -bromonitro compound **250** with amine **251** under standard umpolung amide synthesis conditions led to formation of dipeptide **252** in good yield (**Scheme 77**). Deprotection and standard amide coupling of pyridine carboxylic acid **253** afforded **254** in good yield over two steps.



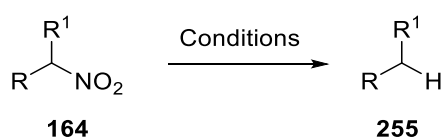
**Scheme 77.** Synthesis of **254** via Johnston's umpolung (Nef) amide formation

## 1.4. Radical Denitration

### 1.4.1 Overview

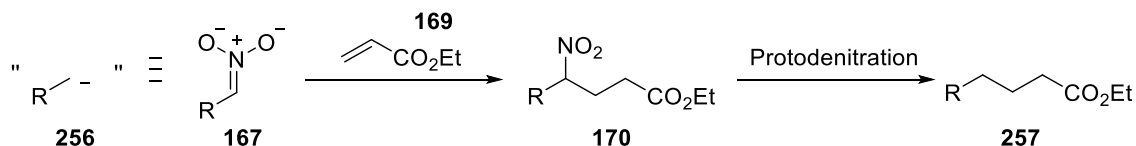
The use of radicals in organic chemistry is well documented, often as a complementary tool for the installation or removal of functional groups, or formation of carbon-carbon bonds. The use of one-electron processes can afford many benefits. Unlike some of their ionic counterparts, radicals do not promote epimerization of acidic stereocentres, do not command a large solvent sphere and are able to more easily penetrate hindered or polar environments as they are uncharged. In addition the larger energy required for homolysis of some polar bonds effectively 'protects' some functional groups usually reactive under ionic conditions, for example hydroxyl, amino and carbonyl groups.<sup>137</sup>

Radical denitration was discovered over 35 years ago and has proven an extremely useful modification to the nitro group in synthesis.<sup>49a</sup> The removal of the nitro group results in the formation of a carbon centred radical; this radical can then undergo rearrangement, form a new carbon-carbon bond or simply undergo hydrogen abstraction (protodenitration) (**Scheme 78**).



**Scheme 78.** Radical protodenitration

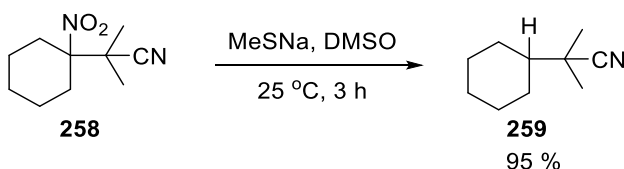
Radical chemistry provides the opportunity for the nitronate anion to be viewed as a carbanion surrogate (**Scheme 79**). As discussed in previous chapters, the nitro group readily stabilises adjacent negative charge, with addition to electrophiles providing many pathways for the formation of new carbon-carbon bonds.



**Scheme 79.** Use of nitroalkanes as carbanion surrogates

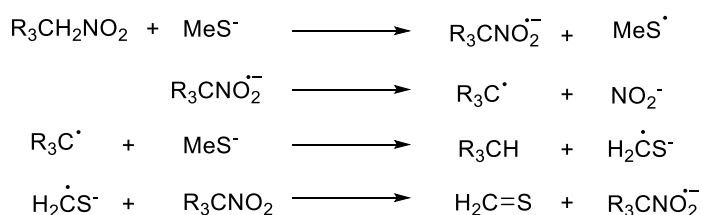
#### 1.4.2 Protodenitration - Initial discovery

The first reported radical protodenitration was published by Kornblum in 1978 (**Scheme 80**).<sup>75c, 138</sup> Denitration of tertiary nitro compounds by the sodium salt of methyl mercaptan (MeSNa) was reported in high yields in DMSO, DMF or HMPA.



**Scheme 80.** An example of the first radical protodenitration reaction by Kornblum

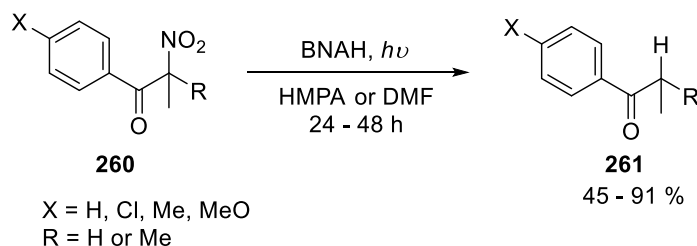
The reaction is thought to proceed by SET from  $\text{MeS}^-$  to the nitro group affording a radical anion; loss of  $\text{NO}_2^-$  then generates a carbon centred radical which undergoes hydrogen abstraction to give the product (**Scheme 81**). A competitive reaction in which the thioether is formed results under the use of certain solvents.<sup>75c</sup>



**Scheme 81.** SET mechanism for protodenitration using MeSNa

A range of reagents which effect radical protodenitration via a SET mechanism analogous to that of MeSNa were discovered within a ten year window. These include KOH/ethylene glycol,<sup>139</sup> 1-benzyl-1,4-dihydronicotinamide (BNAH)/ $h\nu$  (**Scheme 82**),<sup>140</sup> and sodium telluride (NaTeH).<sup>141</sup> Many of these reactions are however limited to a few examples of protodenitration of tertiary<sup>75c, 138-139, 141</sup> or activated<sup>140</sup> (adjacent to an

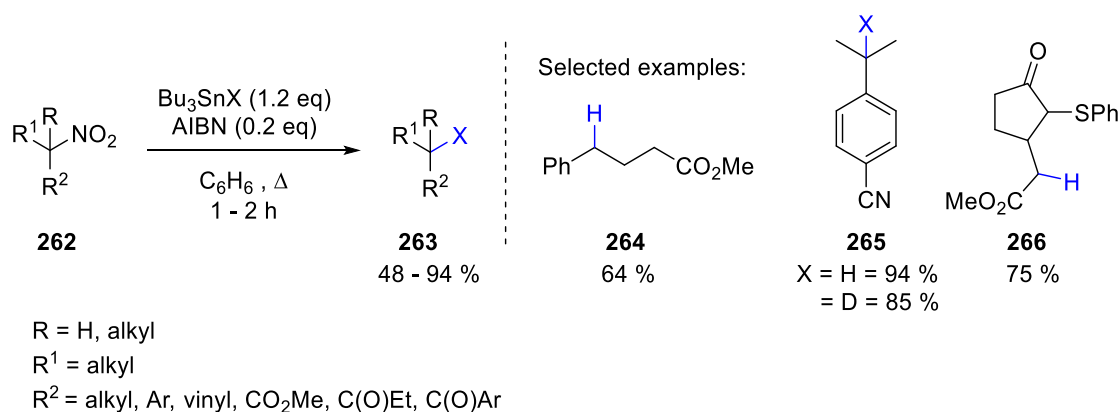
electron stabilising group) nitro groups. Protodenitration using BNAH requires an  $\alpha$ -activating group; both secondary and tertiary nitro groups are reduced in moderate to excellent yields (**Scheme 82**). A range of functional groups are tolerated, however bromides and sulfones are selectively reduced by BNAH in the presence of the nitro group.<sup>140</sup>



**Scheme 82.** Protodenitration using BNAH

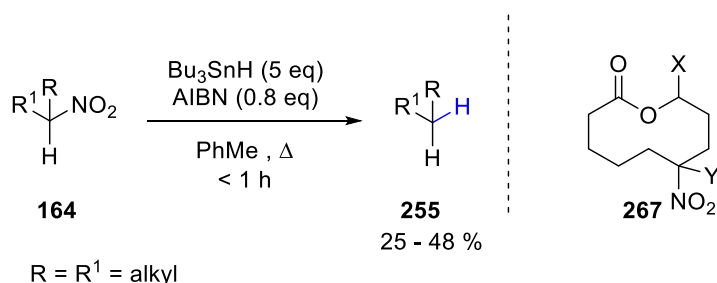
In 1981 the groups of Ono<sup>142</sup> and Tanner<sup>143</sup> independently published results naming tri-*n*-butyltin hydride (TBTH) as an efficient reagent for the protodenitration of tertiary or activated secondary nitro compounds. Tanner reported a procedure for the denitration of tertiary nitro compounds using TBTH (3 eq) and benzoyl peroxide (8 – 12 mol %) at reflux in benzene. A small range of compounds were reported, with only one reported isolated yield for compound **265** (X = H, 75 %). Ono reported a wide range of nitro compounds which underwent protodenitration in moderate to excellent yields (**Scheme 83**). Ono noted tertiary compounds underwent denitration and replacement with hydrogen (or deuterium using Bu<sub>3</sub>SnD) using 1.2 eq TBTH and a catalytic amount of AIBN as an initiator, refluxing in benzene. The procedure showed improvements over those previously described<sup>75c, 138-141</sup> including reduced reaction times, good chemoselectivity, generality and high yields. Secondary nitro compounds were also reduced under the same conditions when activated by an adjacent electron stabilising group (e.g. aryl, alkenyl, carbonyl). Selective reduction of the nitro group in the presence of carbonyls/nitriles/chlorides/sulfones/sulfur compounds was noted. This is important as the reduction of sulfur compounds with Bu<sub>3</sub>SnH/AIBN is known,<sup>144</sup> however the nitro group is reduced in preference.<sup>142</sup>





**Scheme 83.** Ono's reduction of nitro compounds using tri-*n*-butyltin hydride

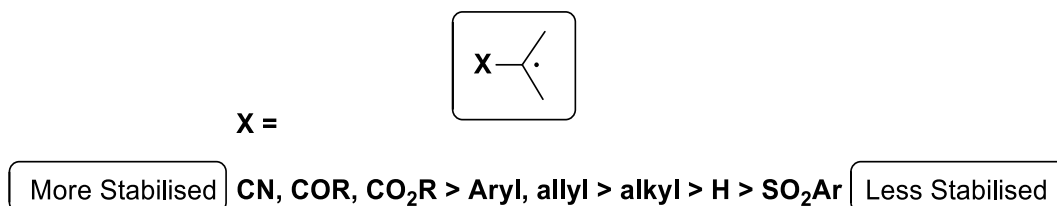
Under the conditions reported (**Scheme 83**), denitration of primary and unactivated secondary nitro compounds was found to be unsuccessful. Only a trace amount of protodenitration occurred (entry 1, **Table 1**), with the remaining products remaining unidentified, probably resulting from non-cleavage of the C-N bond. Extension of protodenitration to unactivated secondary nitro compounds **267** required an increase in the equivalents of TBTH (5 eq), AIBN (0.8 eq) and the reaction was carried out at higher temperature in toluene (**Table 1**).<sup>145</sup> Even under these harsh conditions, yield of the protodenitrated compounds **255** were low compared to similar tertiary compounds (entry 2 vs 4, **Table 1**).



**Table 1.** Variation in yield depending on nitro compound structure and methodology used

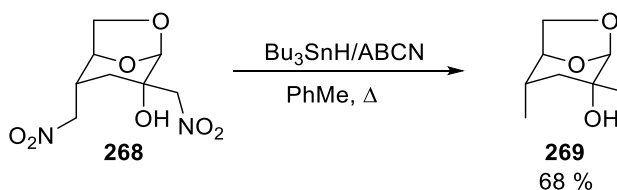
Entry	X	Y	TBTH eq	AIBN eq	solvent	% Yield 255
1	H	H	1.3	0.3	C <sub>6</sub> H <sub>6</sub>	Trace
2	H	H	5	0.8	PhMe	26
3	Me	H	5	0.8	PhMe	48
4	H	CH <sub>2</sub> OAc	1.3	0.3	C <sub>6</sub> H <sub>6</sub>	88

In relation to the effect of hyperconjugative donation of proximate C-H bond electron density to a nearby electron deficient carbon radical, the order of reactivity is tertiary > secondary > primary as expected; ease of protodenitration follows this trend. Activation of secondary nitro groups by adjacent electron stabilising groups follows the order shown below (**Fig. 5**), in which mesomerically stabilising groups such as CN, C(O)R and CO<sub>2</sub>R afford the highest stabilisation, and a destabilising effect is produced by an adjacent sulfonyl group.<sup>146</sup>



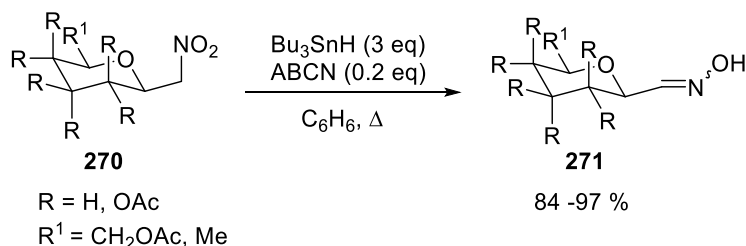
**Fig. 5.** Extent of stabilisation of a carbon radical by an adjacent 'X' group

In fact, only one example of reduction of a primary nitro group exists (**Scheme 84**),<sup>147</sup> and others have cast doubt upon its validity.<sup>49a</sup> Reduction of dinitromethylpyran **268** with TBTH and 1,1'-Azobis(cyclohexanecarbonitrile) (ABCN) in toluene at reflux affords dimethyl compound **269** in good yield (**Scheme 84**). The equivalents of TBTH and ABCN are not given.<sup>147</sup> Usually the primary radical that would form from scission of the C-N bond is so unstable that C-N cleavage does not occur, instead the N-O bond is broken to give the nitroso compound, which rearranges to the oxime (**Scheme 86**).



**Scheme 84.** Radical protodenitration of a primary nitro compound by TBTH

Formation of the oxime occurs in other examples.<sup>148</sup> Petruš detailed the first report of conversion of glycopyranosylnitromethanes **270** to their corresponding oximes **271** in excellent yields using excess TBTH and catalytic ABCN (**Scheme 85**). This alternative mechanistic pathway has proved more effective for the generation of oximes, in high yields rather than protodenitrated products. Less TBTH (3 eq) is required than for cleavage of the C-N bond in secondary nitro compounds (5 eq).<sup>148a, b</sup>

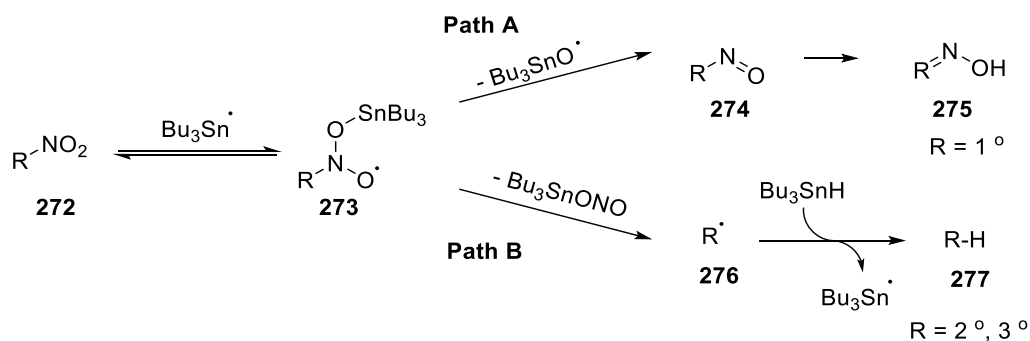


**Scheme 85.** Radical denitration of a primary nitro compound to give an oxime

An example of a hydroxylamine formed from TBTH reduction of hindered nitro groups is thought to proceed in a similar fashion with *in situ* reduction of the nitroso compound by TBTH as tautomerisation to the oxime cannot occur.<sup>149</sup>

### 1.4.3 Mechanism of radical protodenitration using TBTH

Mechanistic studies of the reduction of nitro compounds by TBTH established the presence of a radical chain as the reaction is inhibited by radical inhibitor *m*-dinitrobenzene and promoted by radical initiators.<sup>142-143</sup> Further investigations probed the two hypothesised pathways; SET transfer to give a radical anion followed by loss of  $\text{NO}_2^-$  as described for reactions with MeSNa or BNAH (**Scheme 81**) or formation of a nitroxide radical, followed by cleavage of the C-N bond. The mechanistic pathway taken, as previously stated, depends on the nature of the nitro compound. Tertiary nitro groups are generally less reactive towards TBTH than I, Br, SePh and primary/secondary xanthate esters, but more reactive than Cl or SPh.<sup>150</sup> Reduction of tertiary and secondary nitro groups was found to proceed via addition of the TBTH radical to the nitro group, generating nitroxide radical **273**. Cleavage of the C-N bond affords carbon radical **276** with elimination of  $\text{Bu}_3\text{SnONO}$ , subsequent hydrogen abstraction from TBTH regenerates the radical chain carrier (Path B, **Scheme 86**).<sup>151</sup> Addition of the TBT radical to the nitro group is fast and reversible, cleavage of the C-N bond is rate-limiting.<sup>151a</sup> Stability of the carbon-centred radical formed via this process is essential for chain propagation, hence non-activated secondary nitro compounds have a larger energy barrier to overcome and require forcing conditions. The instability of primary radicals means primary nitro groups undergo N-O bond scission in this case (Path A, **Scheme 86**).<sup>49a, 152</sup> Cleavage of the N-O bond generates nitroso compound **274** which tautomerises to the oxime **275**.

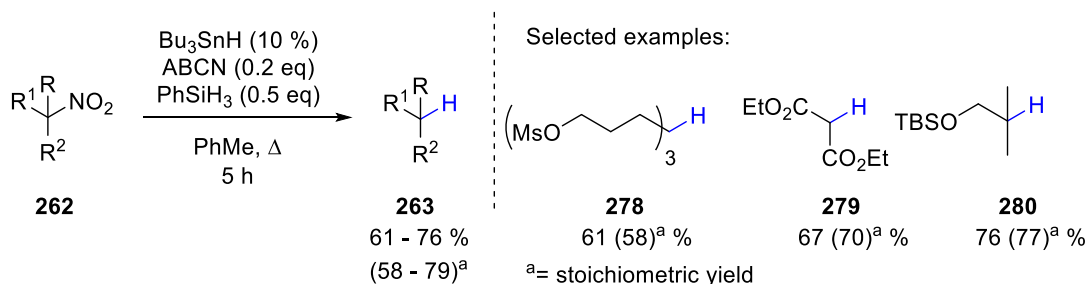


**Scheme 86.** Mechanism of radical protodenitration using TBTH

#### 1.4.4 Other methods for radical protodenitration

A quick search of the literature for non-ionic denitration confirms TBTH as the method of choice for radical mediated denitration; it is efficient, reliable and general, and its specificity is impressive. However organotin compounds are very toxic, and their separation and disposal pose problems,<sup>153</sup> particularly when used in large excesses (5 eq TBTH for secondary nitro reduction). Many other common reagents for the radical removal of functional groups including tris(trimethylsilyl)silane,<sup>154</sup> carbon centred<sup>155</sup> and boryl<sup>152</sup> radicals, are unsuitable, proceeding via cleavage of the N-O bond (analogous to Path A, **Scheme 86**).

The use of TBTH in catalytic quantities (10 %) with PhSiH<sub>3</sub> (0.5 eq) for the reduction of nitro compounds was reported by Fu in 1998.<sup>156</sup> This method is successful for tertiary and activated secondary nitro compounds, with close matching of yields achieved using stoichiometric TBTH (**Scheme 87**). The mechanism proceeds via the Path B mechanism (**Scheme 86**) with reduction of Bu<sub>3</sub>SnONO by PhSiH<sub>3</sub> to regenerate Bu<sub>3</sub>SnH, which re-enters the catalytic cycle.



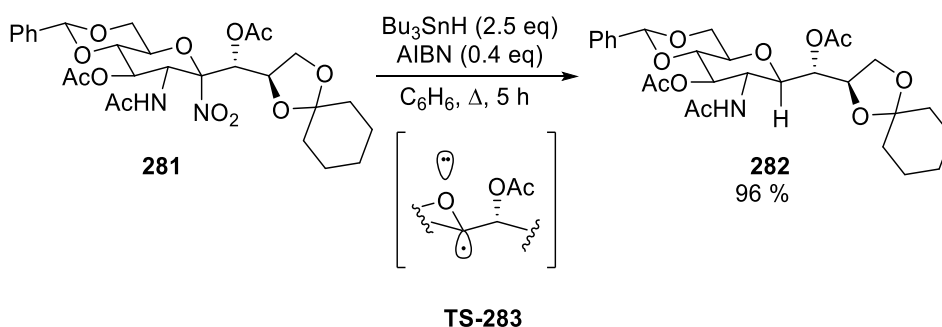
**Scheme 87.** – Reduction of 3° or activated 2° nitro compounds to alkanes using catalytic TBTH and PhSiH<sub>3</sub>

The protodenitration of nitro compounds with TBTH has been widely studied and many examples of this transformation exist.<sup>49a, 157</sup> A review of some of these reactions of  $\beta$ -nitroamine derivatives is given below, followed by their use in synthesis.

#### 1.4.5 Radical protodenitration of $\beta$ -nitroamines

The protodenitration of  $\beta$ -nitroamines and their derivatives is important in synthesis as it allows complex structures to be built up around an amine, with the nitro group facilitating the attack of an alkyl anion equivalent on an imine. Addition of nitronates to imines can be performed selectively via the nitro-Mannich reaction; removal of the nitro group via radical denitration affords the amine, without degradation of existing stereocentres.<sup>4, 157b</sup>

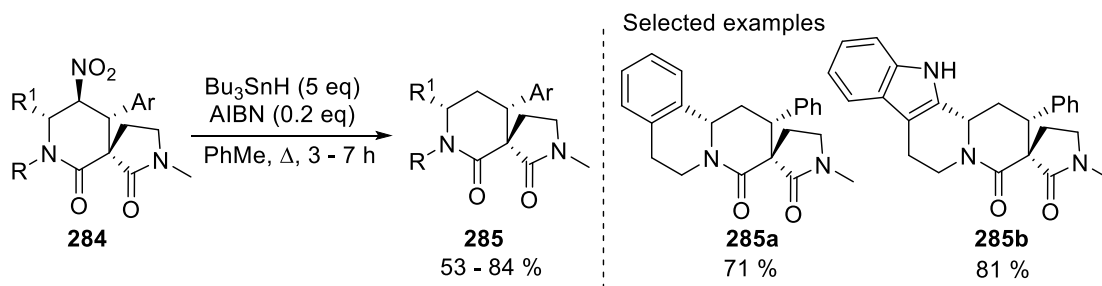
Radical denitration of the  $\beta$ -nitroamide functional group is important for the formation of *pseudo*-aminosugars.<sup>158</sup> In this case, Michael addition of various nitrogen nucleophiles to nitroalkenes or nucleophilic substitution afforded the unactivated secondary  $\beta$ -nitroamides. Protodenitration occurred with moderate to good yields (48 – 77 %); in the case of sugar derivative **281**, an anomalous high yield of 96 % was achieved.<sup>158d</sup> In contrast to the *pseudo*-aminosugars which are not pyran based (cyclohexyl ring), the anomeric position of the nitro group in this glucose-based ring likely accounts for the high yield. Radicals  $\alpha$ -to an oxygen atom in a pyran ring are known to be stabilised by the electron density in the lone pair on oxygen (**TS-283**, **Scheme 88**), this also results in stabilisation of the radical in the axial position, hence hydrogen abstraction at this position by the radical leads to the preferred formation of **282** over its axially-substituted isomer.<sup>159</sup>



**Scheme 88.** Radical protodenitration of an *N*-Acetyl glucose derivative

Protodenitration of cyclic  $\beta$ -nitroamine derivatives **284** by Dixon was achieved under standard conditions for the denitration of unactivated secondary nitro compounds (**Scheme 89**). Tetra- and pentacyclic piperidine-2-one products **285** were afforded in good

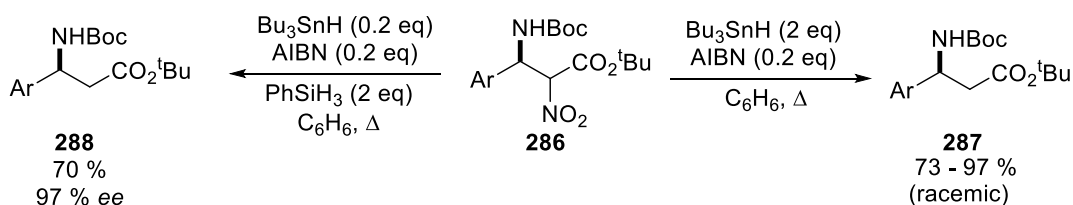
yields. Dixon has shown a range of examples detailing protodenitration of various cyclic unactivated secondary  $\beta$ -nitroamine derivatives.<sup>160</sup>



**Scheme 89.** Protodenitration of 5-nitropiperidine-2-one derivatives

The use of tertiary<sup>161</sup> and activated secondary<sup>162</sup>  $\beta$ -nitroamine derivatives derived from the nitro-Mannich reaction as substrates for protodenitration under milder conditions has been reported. In particular, ‘acetic acid equivalent’  $\alpha$ -nitroesters **286** function as excellent reagents for activation of the nitro group to denitration.

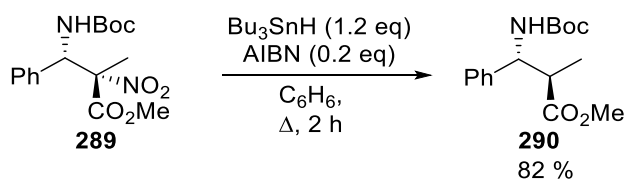
Johnston reported the use of <sup>t</sup>butyl nitroesters with aryl imines to form *N*-Boc protected  $\beta$ -nitro- $\alpha$ -aminoesters **286**.<sup>162</sup> Racemic  $\beta$ -nitro- $\alpha$ -aminoesters underwent protodenitration with a twofold excess of TBTH and catalytic AIBN to give  $\beta$ -amino esters **287** in high yields (**Scheme 90**).<sup>162</sup> The formation of enantioenriched  $\beta$ -nitro- $\alpha$ -aminoesters **286** was also achieved via an organocatalytic reaction; protodenitration afforded the corresponding enantioenriched  $\beta$ -aminoesters **288** with no erosion in *ee* (85 – 98 %) and good yield over two steps (64 – 88 %). An alternative methodology catalytic in TBTH (20 mol %) using phenylsilane as a reducing agent (2 eq)<sup>156</sup> was attempted as an effort to reduce tin waste. The reaction was found to proceed with good yield and no loss of *ee* as expected.



**Scheme 90.** Radical denitration of  $\beta$ -nitro- $\alpha$ -aminoesters using TBTH in excess or catalytically with phenylsilane as a reductant in excess

Li and Chen reported the formation of quaternary centres via the nitro-Mannich addition of methyl substituted  $\alpha$ -nitroesters to *N*-Boc imines to give  $\beta$ -nitro- $\alpha$ -aminoesters **289**. Under standard conditions for protodenitration of tertiary nitro groups,  $\beta$ -nitro- $\alpha$ -

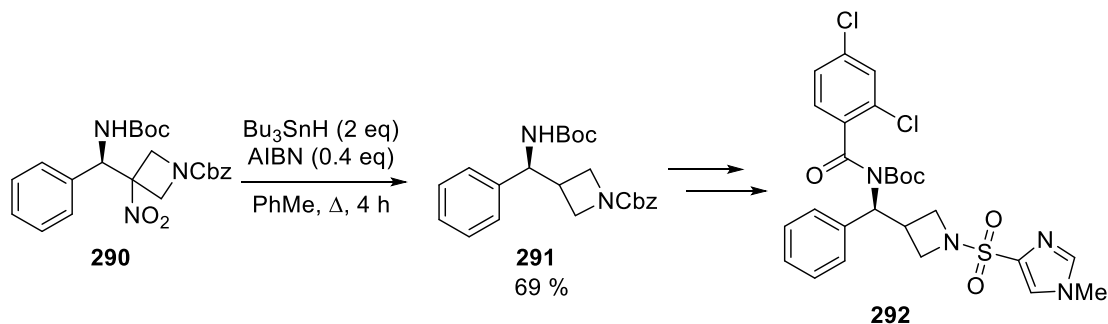
aminoester **289** afforded product  $\beta$ -aminoester **290** in excellent yield (**Scheme 91**).<sup>161b</sup> This methodology allows for the formation of substituted  $\beta$ -aminoesters, building upon Johnston's synthesis of primary  $\beta$ -aminoesters.



**Scheme 91.** Protodenitration of a tertiary  $\beta$ -nitro- $\alpha$ -aminoester using TBTH

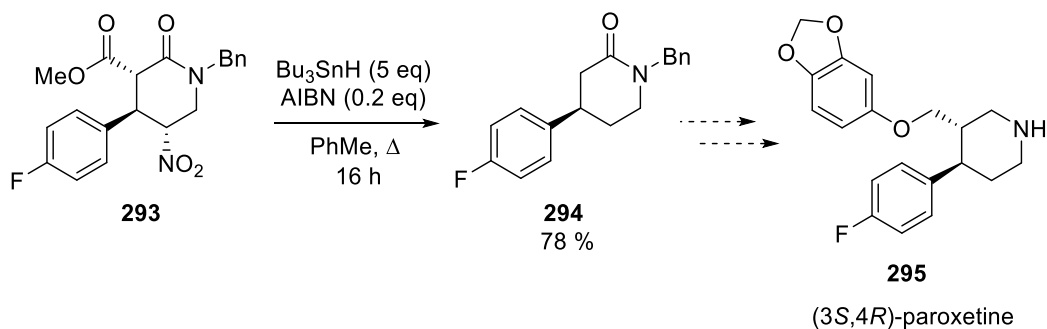
#### 1.4.6 Radical protodenitration of $\beta$ -nitroamines in synthesis

The nitro-Mannich reaction followed by radical protodenitration of the formed  $\beta$ -nitroamine derivative has been used in the synthesis of natural products and biologically active compounds. Johnston reported the synthesis of potent GlyT1 inhibitor **292** via denitration of *N*-Boc protected  $\beta$ -nitroamine derivative **290**.<sup>163</sup> Protodenitration of the tertiary nitro compound proceeds in good yield using a twofold excess of TBTH to afford intermediate  $\alpha$ -aminoazetidine **291** (**Scheme 92**). A further five steps afforded GlyT1 inhibitor **292**.



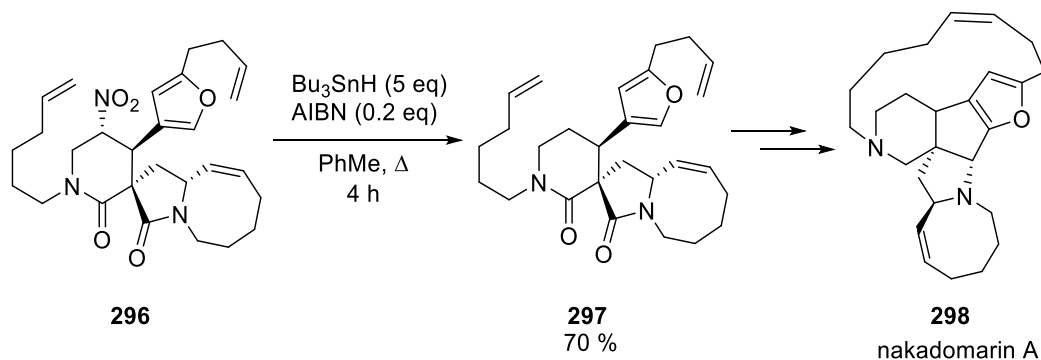
**Scheme 92.** Synthesis of a potent GlyT1 inhibitor via radical protodenitration of an *N*-Boc protected  $\beta$ -nitroamine

Dixon reported a formal synthesis of SSRI anti-depressant (3*R*,4*S*)-paroxetine **295**, centred around his nitro-Mannich/lactamisation cascade reactions methodology.<sup>160c</sup> Protodenitration of unactivated secondary polyfunctional 3-nitropiperidin-2-one **293** with TBTH (5 eq) and catalytic AIBN in toluene afforded denitrated piperidin-2-one **294** in very good yield (**Scheme 93**). Interestingly, under the reaction conditions, a concomitant decarboxylation took place. This does not pose a problem to further synthesis of (3*R*,4*S*)-paroxetine, however this example demonstrates that the forcing conditions required for protodenitration can be incompatible with sensitive functional groups.



**Scheme 93.** Formal synthesis of SSRI anti-depressant (3*S*,4*R*)-paroxetine via protodenitration of a nitrolactam to give a piperidine-2-one intermediate

Dixon has reported similar strategies for intermediates in the total syntheses of manzamine A **247e** (Scheme 75) and nakadomarin A **298** (Scheme 94). Intermediate  $\beta$ -nitroamine derivative 3-nitropiperidine-2-one **296** was reduced directly to the corresponding piperidine-2-one **297** in good yield. Nakadomarin A was achieved in a further three steps from protodenitrated intermediate **297**.<sup>160d</sup> An alternative strategy for the synthesis of nakadomarin A by Dixon requires harsher conditions (reflux in mesitylene, 165 °C, 2.5 h) and gives a slightly lower yield of 65 %.<sup>160e</sup>



**Scheme 94.** Total synthesis of nakadomarin A via protodenitration of a 3-nitropiperidine-2-one intermediate

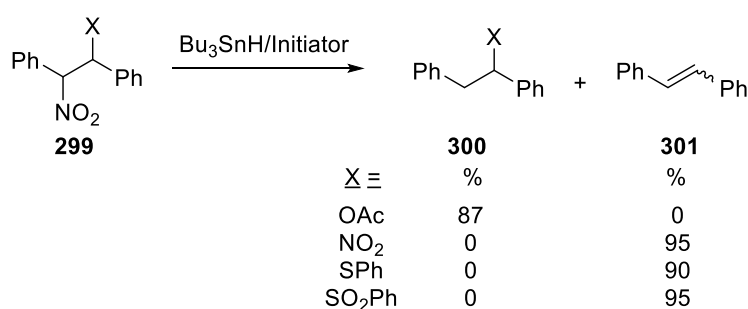
#### 1.4.7 Radical elimination

Alkene formation via  $\beta$ -scission of a radical generated by denitration is possible when the molecule contains a vicinal leaving group. A knowledge of radical leaving groups is important to avoid this elimination process; or to harness it. The use of radical denitration-elimination ( $\beta$ -scission) processes to form an alkene is an alternative to the ionic elimination of nitrous acid. It does not require the presence of vicinal acidic protons, however an appropriate radical leaving group is necessary. An advantage of radical



elimination is that a base is not required; the reaction is run under neutral conditions hence it is more compatible with delicate functional groups and epimerisable stereocentres.

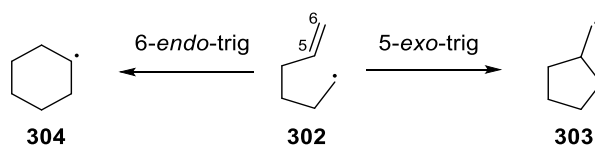
A study by Ono<sup>146</sup> showed that  $\beta$ -scission occurred where  $X = \text{NO}_2$ , SPh and  $\text{SO}_2\text{Ph}$  to form alkene **301** (Scheme 95), other good radical leaving groups are preferentially reduced by the TBTH.<sup>150a</sup> Intramolecular elimination of the radical leaving group is faster than intermolecular hydrogen abstraction, as evidenced by the exclusive formation of **301**. It was found that when  $X = \text{OAc}$ ,  $\beta$ -scission does not occur, the protodenitration product **300** is formed with no trace of alkene **301**. This is due to the instability of the oxygen radical formed and the strength of the C-O bond.



**Scheme 95.** Elimination of radical leaving groups following denitration by TBTH

#### 1.4.8 Intramolecular cyclisation reactions

The addition of radicals to a range of carbon-carbon or carbon-heteroatom multiple bonds is an important tool for the synthesis of new carbon-carbon bonds. Intramolecular cyclisations are widely investigated reactions; cyclisation viability and selectivity of known substituted tethered radical traps (alkenyl, alkynyl or C-X multiple bond variants) can often be predicted.<sup>150b</sup> An example of this, the cyclisation of 5-hexenyl radicals **302** occurs with high preference for the cyclopentyl ring formation (**303:304** = 50:1, **Scheme 96**) due to better orbital overlap of the radical SOMO with the  $\pi^*$  orbital of the alkene.<sup>164</sup>



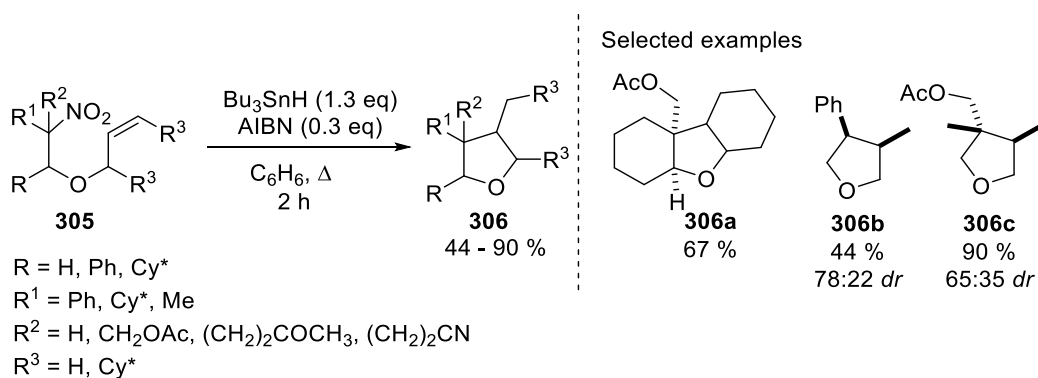
**Scheme 96.** Addition of a radical to an alkene tether

For a cyclisation to be successful, a range of considerations must be satisfied. The radical precursor group (e.g. Br/I/ $\text{NO}_2$ ) must be removed at a sufficient rate that efficient propagation of the chain occurs, and cyclisation of the radical must be faster than

abstraction of hydrogen from TBTH.<sup>150b</sup> Factors that influence the rate and mode of cyclisation include length and substitution pattern of the carbon chain. Methyl-substitution at C-6 favours 5-*exo*-trig cyclisation (>200:1), whereas substitution of C-5 renders 6-*endo*-trig more favourable (36:64).<sup>165</sup>

Radical denitration by TBTH has been shown by Ono to be a useful method for the generation of radical species.<sup>142</sup> Extension of this method to the formation of carbon-carbon bonds was also reported, with intramolecular addition of tertiary radicals to both alkenes and alkynes.<sup>146</sup> As previously stated, the nitro group can be used as an 'alkyl anion equivalent' undergoing addition of a nitronate to C=X bonds or 1,4-addition reactions.<sup>157b</sup> The formation of radicals via denitration adds another dimension as the nitro group is lost *in situ* whilst undergoing carbon-carbon bond formation. Denitration of tertiary nitro groups in particular is very useful, as the tertiary radical formed is uniquely placed to form a quaternary centre with more ease than its ionic equivalent.<sup>165</sup>

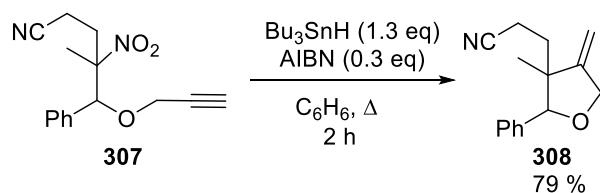
Initial investigations by Ono<sup>146</sup> probed the cyclisation of ether-tethered alkenes and alkynes prepared via addition of the corresponding sodium alkoxide to a nitroalkene. Denitration followed by 5-*exo*-trig cyclisation afforded the tetrahydrofuran (THF) products **306** in moderate to excellent yields (**Scheme 97**).



**Scheme 97.** The first radical denitration-cyclisation reactions of tethered alkenes

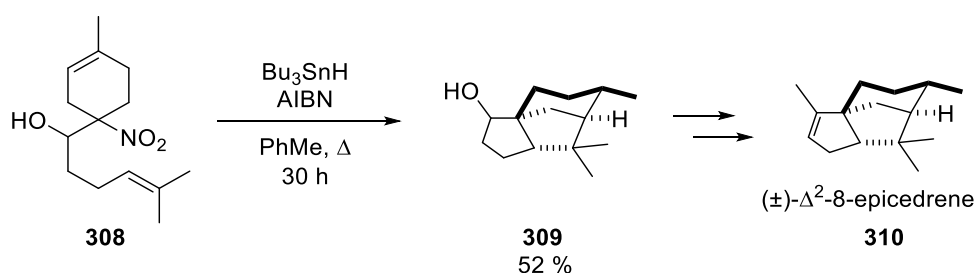
The formation of a *cis*-ring junction for tricyclic THF **306a** is expected due to ring strain. Disubstituted THF **306b** is formed from an activated secondary nitro compound (**305b**,  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ), which may account for the lower yield. Radical cyclisation of 6-bromo-6-phenyl-1-hexene is known to give *trans*-selectivity of the formed cyclopentane in contrast to the usual *cis*-disubstituted cyclopentane rings observed;<sup>164b</sup> in the case of disubstituted THF **306b** the *cis*- stereochemistry is favoured. Trisubstituted THF **306c** is formed in excellent yield, attributed to the formation of a tertiary radical, however with

low *dr*. It is difficult to predict expected stereo-outcomes in the case of densely substituted radical centres.<sup>146</sup> Denitration followed by 5-*exo*-trig cyclisation of tethered alkyne **307** was also successful, *exo*-alkenyl-THF **308** was formed in very good yield (**Scheme 98**).



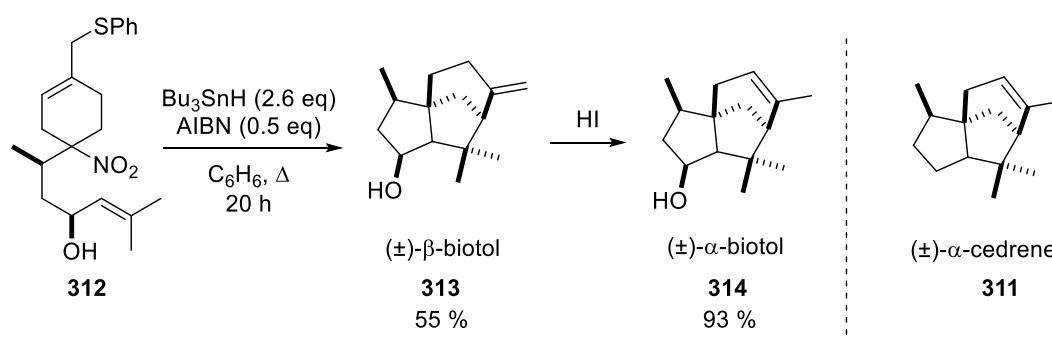
**Scheme 98.** The first radical denitration-cyclisation reaction of a tethered alkyne

Vankar also reported a similar radical cyclisation of a propargylic ether derivative a few years later.<sup>166</sup> A major development in the use of radical denitration-cyclisation was shortly followed by Chen, who reported a selection of tandem radical cyclisations for the synthesis of sesquiterpenes or their precursors.<sup>167</sup> The methodology involved the initial formation of tethered alkene tertiary nitroalcohol **308** followed by cyclisation via the conditions described by Ono<sup>157a</sup> to give the tricyclic scaffold **309** in good yield (**Scheme 99**). A further four steps furnished ( $\pm$ )- $\Delta^2$ -8-epicedrene **310**.<sup>167a</sup>



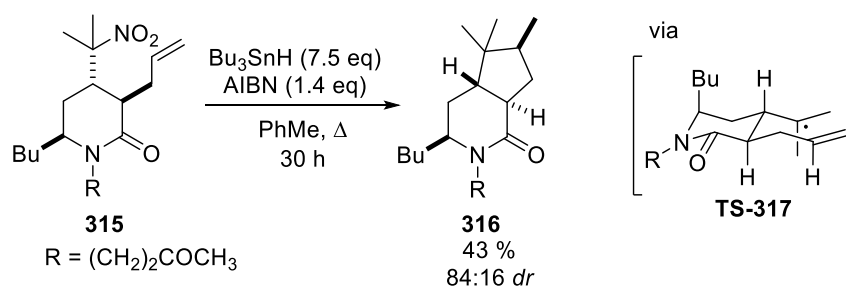
**Scheme 99.** Tandem denitration-cyclisation reaction and generation of a tricyclic sesquiterpene

Further elaboration of this methodology by Chen resulted in the formal synthesis of ( $\pm$ )- $\alpha$ -cedrene **311**,<sup>167b</sup> and total syntheses of ( $\pm$ )- $\alpha$ -biotol **314** and ( $\pm$ )- $\beta$ -biotol **313**<sup>167c</sup> via a tandem radical cyclisation-elimination sequence from tertiary nitro compound **312**. The cyclisation-elimination sequence proceeded with high stereoselectivity, affording ( $\pm$ )- $\beta$ -biotol **313** in good yield (**Scheme 100**); it was postulated that the cyclisation proceeds via a chair transition state with both methyl and hydroxyl groups equatorial.<sup>167c</sup> Isomerisation of the double bond affords ( $\pm$ )- $\alpha$ -biotol **314** in excellent yield.



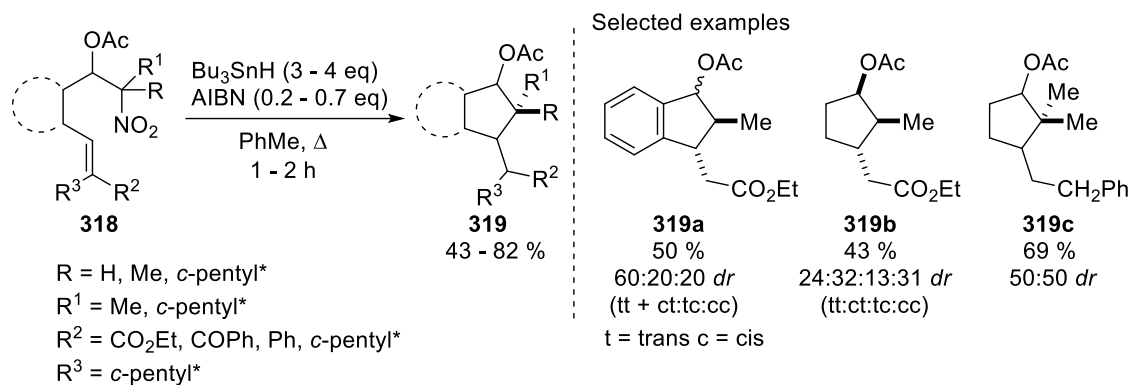
**Scheme 100.** Tandem denitration-cyclisation-elimination reaction and generation of tricyclic sesquiterpenes

Further studies by Chen include radical denitration followed by 6-*endo*-dig cyclisation on to an  $\alpha$ -allenic ketone.<sup>167d</sup> Sosnicki reported the 5-*exo*-trig cyclisation of a tertiary nitro compound **315** which required a large excess (7.5 eq) of TBTH and stoichiometric AIBN (1.4 eq) to proceed, giving bicyclic pyridin-2-one **316** in moderate yield, however selectivity was high (**Scheme 101**). The reaction is thought to proceed via a chair-like transition state (**TS-317**).<sup>168</sup>



**Scheme 101.** Radical cyclisation of a tertiary nitro compound to give a bicyclic pyridine-2-one derivative

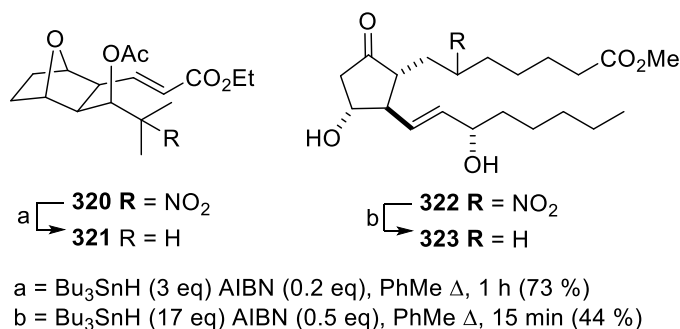
In 2006, Luzzio reported a general radical denitration-cyclisation of Henry adducts with tethered substituted alkenes.<sup>169</sup> Denitration by TBTH followed by exclusive 5-*exo*-trig cyclisation of the radical onto an electron rich or electron poor alkene afforded cyclopentane derivatives **319** (**Scheme 102**). Secondary nitro precursors afforded the corresponding cyclopentane derivatives in lower yields (43 – 50 %), tertiary nitro precursors afforded higher yields (69 – 82 %).



**Scheme 102.** Radical denitration-cyclisations of Henry adducts containing substituted alkenes

The derivatisation of the alkene substrates shows the effects of frontier molecular orbital interactions on the cyclisations. The SOMO of the (tertiary) nucleophilic radical generated from denitration interacts more effectively with the LUMO of the electron deficient alkenes. A lower yield is seen for more electron rich alkenes (69 – 72 %) *c.f.* ethyl acrylates (79 – 82%). Diastereoselectivity of the reaction is low, with the full spectrum of available combinations for each cyclopentane present. Where two chiral centres exist, no or slight preference for *cis*- or *trans*- isomers is seen (40:60 - 60:40 *cis:trans*). Where 3 contiguous stereocentres exist, no discernible major preference for any particular configuration is seen.<sup>169</sup>

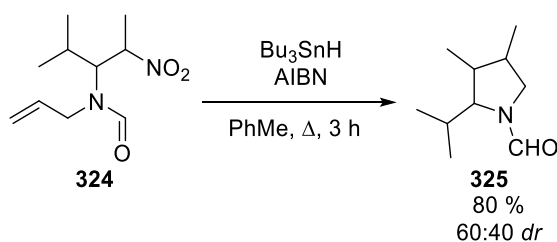
Despite the rapid nature of the 5-hexenyl radical closure, cyclisation does not always occur; competing hydrogen abstraction may take place due to high concentration of TBTH or a slow rate of cyclisation. Rate of hydrogen abstraction is proportional to [Bu<sub>3</sub>SnH], whereas rate remains constant for a given cyclisation, hence adjustment in [Bu<sub>3</sub>SnH] can direct a radical pathway towards cyclisation or abstraction. In the case of 5-hexenyl radical derivative precursors **320** (tertiary) and **322** (secondary) cyclisation does not occur (**Scheme 103**). In the case of nitroacetate **320**, cyclisation with a threefold excess of TBTH may be retarded by a slow rate of cyclisation due to unfavourable geometry;<sup>169</sup> other substrates of a similar type (**Scheme 102**) underwent cyclisation under the same conditions. Cyclisation of 6-nitro-PGE<sub>1</sub> methyl ester **322** is also unsuccessful; the rate of cyclisation may be slow, however a large equivalent of TBTH is used. Under these conditions only the protodenitrated product **323** is isolated (**Scheme 103**).<sup>170</sup>



**Scheme 103.** Unsuccessful radical denitration-cyclisation in favour of protodenitration

#### 1.4.8.1 Radical cyclisation of β-nitroamine derivative

The radical denitration-cyclisation of a β-nitroamine derivative is known, reported by Kamimura<sup>171</sup> in 2006. The β-nitroformamide **324** underwent cyclisation on treatment with an unspecified quantity of TBTH and AIBN in toluene to afford pyrrolidine **325** in very good yield (**Scheme 104**). Only two of a possible four diastereoisomers were observed, with a *dr* of 60:40, but with unknown stereochemistry.

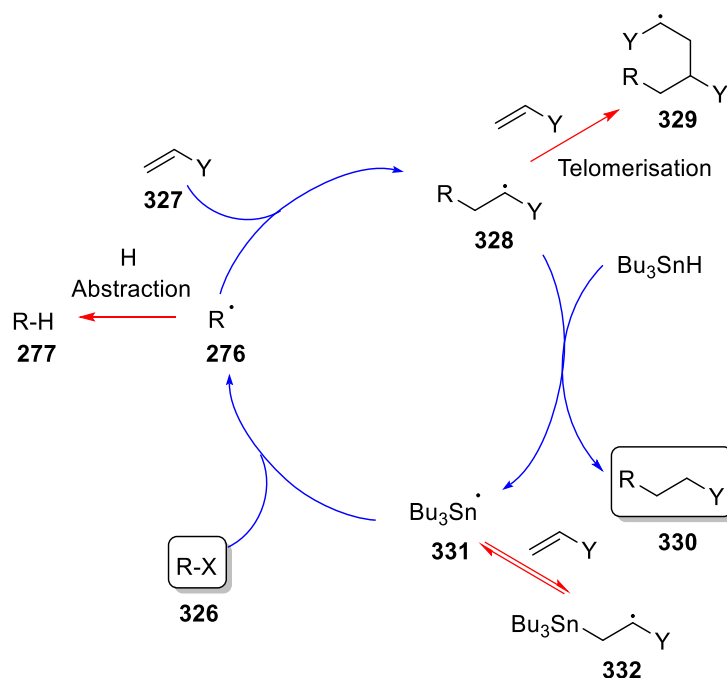


**Scheme 104.** Radical denitration-cyclisation of a β-nitroformamide by Kamimura

#### 1.4.9 Intermolecular addition

The intramolecular addition of radicals to unsaturated bonds is useful for the formation of complex ring systems; however its intermolecular variant not only creates new carbon-carbon bonds, but can prove a powerful step in joining complex molecular fragments together. The application of many of the same considerations is essential for generation of an efficient radical addition chain process, however the intermolecular process is more delicate. The radical precursor group (e.g. I, Br, NO<sub>2</sub>) is especially important for intermolecular addition. The rate of radical removal of 'X' (**Scheme 105**) to generate R radical **276** is important due to competitive addition of the Bu<sub>3</sub>Sn• radical **331** to the alkene to generate adduct radical **332**. Although this addition is reversible, it competes with the removal of X, stalling the chain reaction and can sequester the alkene in an

overall hydrostannylation. This side reaction can be problematic with less reactive species where  $X = -NC, Cl, SPh, 1^\circ/2^\circ$  nitro compounds.<sup>164a, 172</sup>

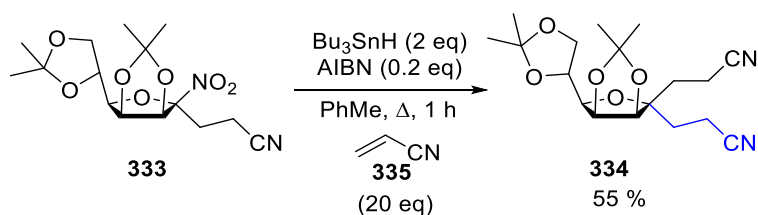


**Scheme 105.** Reaction pathways in the radical addition to alkenes

Another main concern is chain propagation along the correct pathway to form the desired product **330** (**Scheme 105**). Close proximity of a tethered chain to a radical facilitates the unimolecular (*c.f.* bimolecular - hydrogen abstraction step) process under dilution, however a third species is also involved in the intermolecular addition. Reaction must be faster with the desired coupling partner at each step if a viable chain is to occur. Radical **276** must enter the blue pathway undergoing addition to the alkene to generate adduct radical **328** followed by abstraction of hydrogen from TBTH to generate product **330** and regenerate the radical chain carrier **331**.

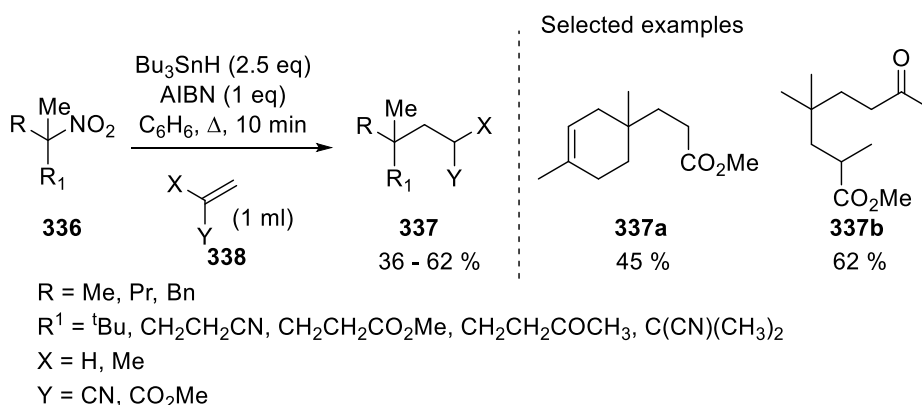
A nucleophilic radical interacts more favourably with an electrophilic alkene and vice versa due to better interaction of the SOMO with the LUMO ( $Y = EWG$ ) or HOMO ( $Y = EDG$ ) of the alkene. This allows for reaction planning; addition of a nucleophilic radical to an electron poor alkene is fast, however the formation of a new electron poor radical **328** then makes further reaction with electron poor species less likely. Telomerisation to give products **329** and yield loss of product **330** are minimised.<sup>172-173</sup> In addition, concentration of TBTH must not be too high, as this could lead to premature trapping of the radical **276** to give protodenitrated by-product **277**.

Ono showed the feasibility of radical denitration of tertiary and secondary nitro groups.<sup>142,</sup>  
<sup>145</sup> The application of this methodology was reported in 1985 by Giese<sup>174</sup> for intermolecular addition of tertiary radicals. Denitration of nitrosugar **333** followed by addition to acrylonitrile **335** (large excess – 20 eq) afforded adduct **334** in good yield (**Scheme 106**). The planar radical formed undergoes addition at the less sterically hindered face, confirmed by deuterium trapping with Bu<sub>3</sub>SnD.



**Scheme 106.** The first radical denitration-intermolecular addition to an alkene

The same year, Ono reported a range of radical intermolecular additions of tertiary nitro compounds **336** to electron poor alkenes **338** in moderate to good yields (**Scheme 107**).<sup>146,</sup>  
<sup>175</sup> This method is useful for the generation of quaternary carbon centres.

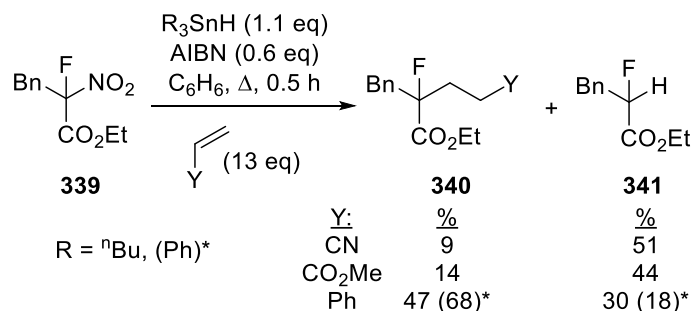


**Scheme 107.** Radical denitration-addition of tertiary nitro groups to alkenes

Takeuchi<sup>176</sup> later reported the denitration-addition reaction of tertiary nitro compounds for the creation of tertiary fluoride compounds **340**. This is an example of reversed electronic interactions; the electrophilic radical generated reacts preferably with electron rich alkenes. Reaction of the fluoride radical with acrylonitrile or methyl acrylate is unfavourable due to the energy mismatch of the SOMO-HOMO interactions. This leads to preferential protodenitration and low yield of the addition product. Electron rich styrene has a HOMO closer in energy to the SOMO of the electrophilic radical, hence a much higher yield of addition product **340** is obtained. Furthermore, when the more



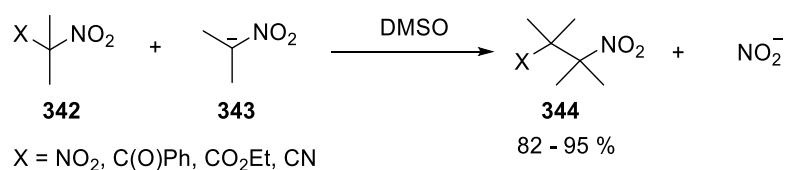
electrophilic tri-phenyltin hydride (TPTH-yield in parentheses) is used, higher yields of addition product **340** are obtained (**Scheme 108**).<sup>176b</sup>



**Scheme 108.** Radical addition of electrophilic radicals to electron rich alkenes

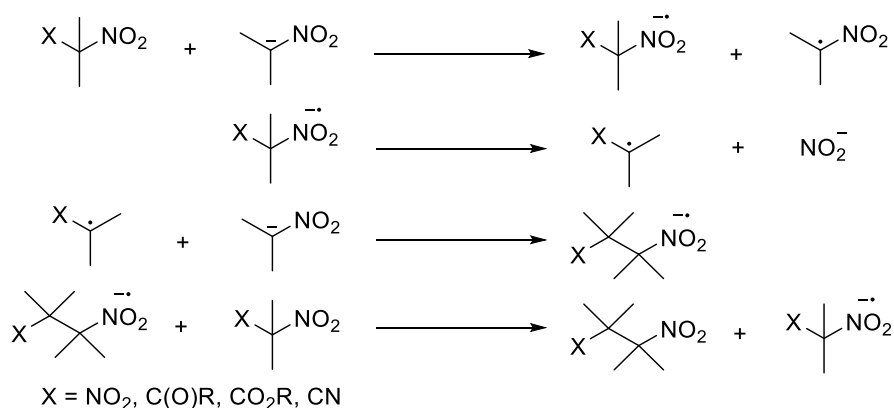
#### 1.4.10 Nucleophilic radical substitution (S<sub>RN</sub>1) of nitro compounds

In 1970, Kornblum<sup>177</sup> reported that  $\alpha$ -substituted dinitro, nitroester, nitroketone or nitronitrile compounds undergo displacement of the nitro group by the salts of nitroalkanes (**Scheme 109**).



**Scheme 109.** S<sub>RN</sub>1 displacement of  $\alpha$ -nitro compounds by 2-nitropropane nitronate salt

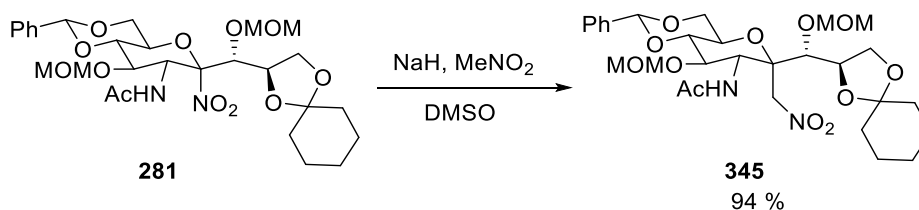
Contrary to the mechanistic pathway taken by radical denitration using TBTH (**Scheme 86**), radical nucleophilic substitution of nitro compounds follows an SET-type denitration pathway akin to that of MeSNa/BNH/KOH-ethylene glycol/NaTeH<sup>75c, 138-141</sup> (**Scheme 81**).<sup>178</sup> In this case, the reaction is initiated by electron transfer from the nitronate salt **343** to the neutral nitro compound **342**, forming a radical anion. Loss of the nitrite anion results in the formation of a radical, which then reacts with another molecule of nitronate **343** to generate a conjugate nitro radical anion. A subsequent SET confers an electron to neutral nitro compound **342**, giving the S<sub>RN</sub>1 product **344** and a radical anion which undergoes further reaction in a chain-type process (**Scheme 110**). This mechanism is supported by complete inhibition of the reaction for several hours, via the addition of *p*-dinitrobenzene (strong electron acceptor) or radical scavenger galvinoxyl, and acceleration of the reaction in the presence of light.<sup>179</sup>



**Scheme 110.** Mechanism of  $\text{S}_{\text{RN}}1$  reaction of  $\alpha$ -substituted nitro compounds

#### 1.4.10.1. Radical nucleophilic substitution ( $\text{S}_{\text{RN}}1$ ) of $\beta$ -nitroamine derivatives

Application of nucleophilic radical substitution ( $\text{S}_{\text{RN}}1$ ) of  $\beta$ -nitroamine **281** in the synthesis of *N*-acetylneuraminic acid analogues was reported by Vasella.<sup>180</sup> Addition of the sodium salt of nitromethane to the  $\beta$ -nitroamine results in clean formation of the nitromethane adduct **345** in excellent yield (**Scheme 111**). Reaction also occurred with high stereospecificity, giving only the axial-substituted nitromethane adduct. This is likely due to the stabilisation of radicals in the axial position due to the anomeric effect as previously described for denitration of **281** (**Scheme 88**).

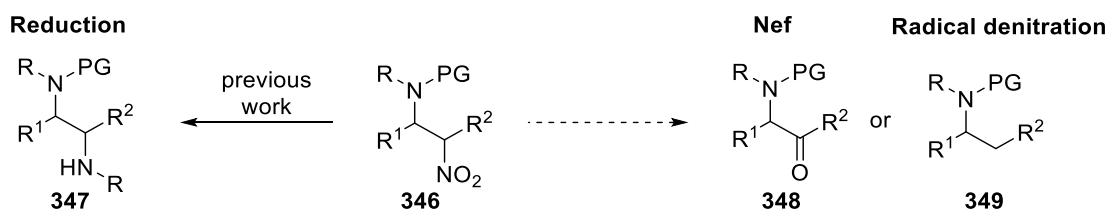


**Scheme 111.** Nucleophilic radical substitution of the nitro group by the sodium salt of nitromethane

## Chapter 2: Results and Discussion

### 2.1 Proposed research

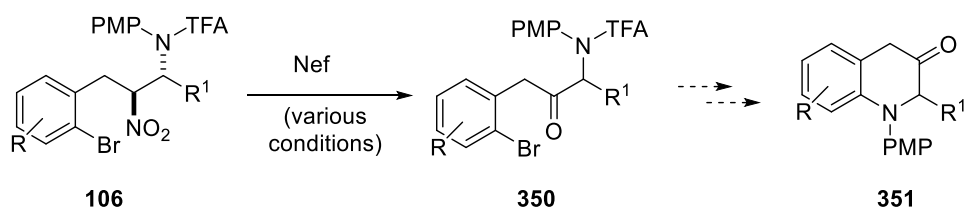
Previous work in the Anderson group has focused on the generation of  $\beta$ -nitroamines via the deprotonative<sup>5</sup> or conjugate nitro-Mannich reaction,<sup>55, 62</sup> followed in most cases by reduction of the nitro group.<sup>5, 14, 55, 62, 65</sup> However expansion of the utility of  $\beta$ -nitroamines or the corresponding *N*-TFA protected derivatives via alternative transformations of the nitro group would showcase the possible uses of the nitro-Mannich reaction in synthesis (**Scheme 112**).



**Scheme 112.** Expansion of the utility of nitro-Mannich products proposed

One example of an attempted Nef reaction in the Anderson group resulted in the formation of a stabilised enol due to conjugation in the molecule (**Scheme 67**).<sup>58</sup> However more successful Nef reactions of  $\beta$ -nitroamine derivatives have been reported by other groups (see section 1.3).

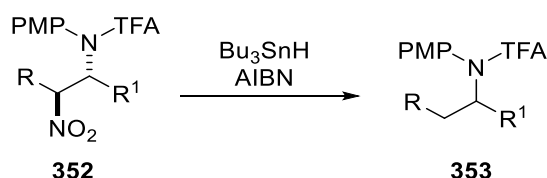
It was envisaged that the Nef reaction could be attempted on  $\beta$ -nitroacetamide derivatives **106**, and if successful, application to the synthesis of tetrahydroquinolin-3-ones **351** could follow (**Scheme 113**). The analogous synthesis of tetrahydroquinolines via Buchwald-Hartwig coupling has been described for orthogonally protected 1,2-diamines.<sup>65</sup>



**Scheme 113.** Derivatisation of  $\beta$ -nitroacetamides – Nef

Radical denitration has been described for a range of  $\beta$ -nitroamine derivatives (See section 1.4). Of particular interest is the denitration of secondary nitro derivatives, which are known to require more forcing conditions,<sup>145</sup> as the  $\beta$ -nitroacetamides generated in this work contain secondary nitro groups.

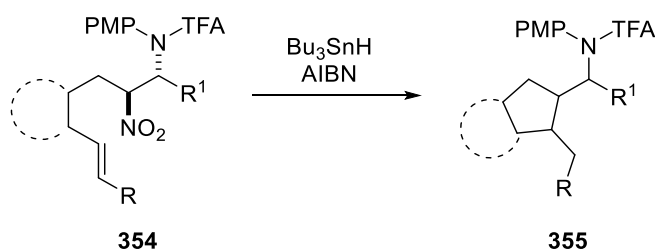
Radical denitration of unactivated secondary nitro groups of  $\beta$ -nitroamine derivatives using excess TBTH has been successfully accomplished by several groups<sup>160, 181</sup> (See section 1.4.4). Application of this methodology to the radical denitration of  $\beta$ -nitroacetamides **352** should lead to the formation of protodenitrated products **353** (**Scheme 114**).



**Scheme 114.** Derivatisation of  $\beta$ -nitroacetamides – Radical denitration

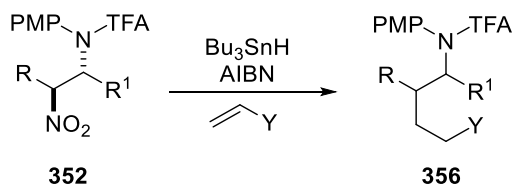
Protodenitrated derivatives **353** do not confer much utility as loss of the nitro group to generate acetamide is atom-inefficient. However, carbon-carbon bond formation would allow the building up of complex chiral amines via the nitro-Mannich-denitration reaction sequence.

Intramolecular cyclisation of nitro compounds is known, with just one example of radical cyclisation of a  $\beta$ -nitroamide (**Scheme 104**).<sup>171</sup> Work by Luzzio<sup>169</sup> on a range of tethered nitro compounds generated via the Henry reaction (**Scheme 102**) supports the possibility of extension to intramolecular cyclisation of tethered-alkene  $\beta$ -nitroacetamides of type **354** (**Scheme 115**).



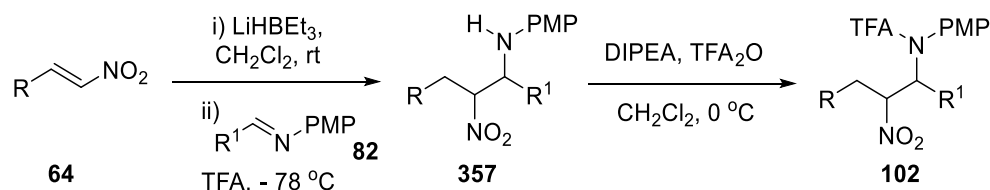
**Scheme 115.** Derivatisation of  $\beta$ -nitroacetamides – Radical denitration-cyclisation

The radical denitration-intermolecular addition to alkenes has been demonstrated using tertiary nitro compounds.<sup>146, 174</sup> Although it has been stated to be unlikely that secondary nitro groups will act as agents for intramolecular radical addition to alkenes due to the slow rate of abstraction of the nitro group compared with side reactions,<sup>150b, 172</sup> attempts at this reaction may prove successful under optimised conditions (**Scheme 116**).



**Scheme 116.** Derivatisation of  $\beta$ -nitroacetamides –Intermolecular radical denitration-addition to alkenes

In order to generate the  $\beta$ -nitroacetamide precursors for these reactions, the reductive nitro-Mannich reaction and *N*-TFA protection steps previously demonstrated in the Anderson group<sup>55, 62, 65</sup> would facilitate access to a range of derivatives by variation of the nitroalkene and imine precursors (**Scheme 117**).



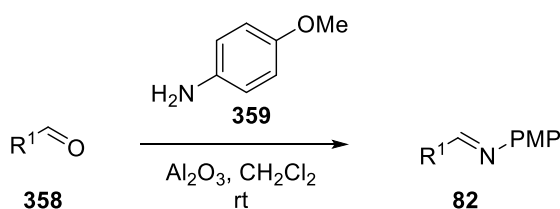
**Scheme 117.** Formation of the  $\beta$ -nitroacetamides

## 2.2 The Nef reaction

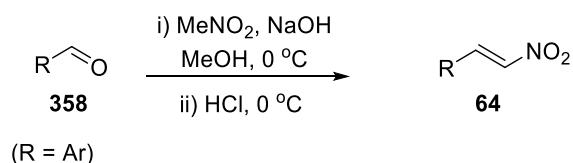
### 2.2.1 Formation of $\beta$ -nitroacetamides

Previous work in the Anderson group has focussed on the base-mediated or conjugate addition nitro-Mannich reactions. Of these two methods, the conjugate addition nitro-Mannich adds more value to the synthesis of  $\beta$ -nitroacetamides due to the installation of a nucleophile at the  $\gamma$ -position.<sup>55</sup> However, our initial investigation of the Nef reaction was conducted on  $\beta$ -nitroacetamides prepared from the reductive nitro-Mannich reaction with hydride as a nucleophile.<sup>62</sup>

Imines **82** were prepared from the corresponding aldehydes **358** via general procedure A (**Scheme 118**). Aryl nitroalkenes **64** were prepared from aryl aldehydes **358** via general procedure B (**Scheme 119**) as previously described within the group,<sup>65</sup> with the exception of commercially available *trans*- $\beta$ -nitrostyrene **64a**.

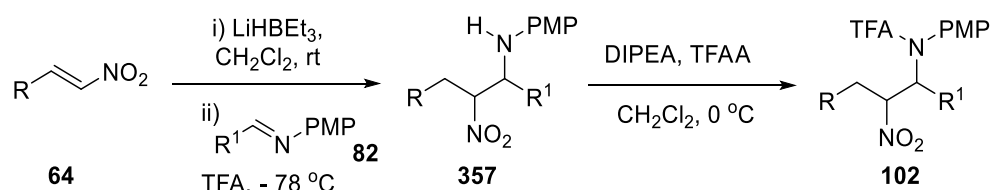


**Scheme 118.** General procedure A for the generation of *N*-PMP imines



**Scheme 119.** General procedure B for the generation of aryl nitroalkenes

The use of 2-bromobenzaldehyde afforded nitroalkene **64b** in 86 % yield, benzaldehyde afforded imine **82a** in 63 % yield. Subjection of *trans*- $\beta$ -nitrostyrene **64a** and nitroalkene **64b** to the reductive nitro-Mannich reaction using LiHBEt<sub>3</sub> and imine **82a** followed by *N*-TFA protection (General procedure F) afforded  $\beta$ -nitroacetamides **102aa** and **102ba** in 66 and 62 % respective yield over two steps (Entries 1 & 2, **Table 2**). In the case of  $\beta$ -nitroacetamides **102aa** & **102ba**, it was found that recrystallization from MeOH/Hexanes affords the product  $\beta$ -nitroacetamides **102** without the need for purification via flash column chromatography. A slightly lower yield was achieved (66 vs 82 %, **102aa** and 62 vs 71 %, **102ba**)<sup>62, 65</sup> (Entries 1 & 2, **Table 2**) however this is a more economical method, less time-intensive and produces less waste. Previous work in this group revealed the *dr* of these reductive nitro-Mannich reactions to be > 95:5 *anti*:*syn*. in this work, a *dr* of >95:5 was also observed after recrystallisation. The  $\beta$ -nitroacetamides are thus described as essentially the *anti*-isomer in line with previous work in the group, and in agreement with data reported in the literature.<sup>62, 65</sup>



**Table 2.** Formation of  $\beta$ -nitroacetamides via the reductive nitro-Mannich reaction

Entry	R ( <b>64</b> ) <sup>a</sup>	R <sup>1</sup> ( <b>82</b> ) <sup>b</sup>	% Yield <sup>c</sup>	<i>dr</i>	Product
1	Ph ( <b>64a</b> )	Ph ( <b>82a</b> )	66	> 95:5	<b>102aa</b>
2	2-BrC <sub>6</sub> H <sub>4</sub> ( <b>64b</b> )	Ph ( <b>82a</b> )	62	> 95:5	<b>102ba</b>

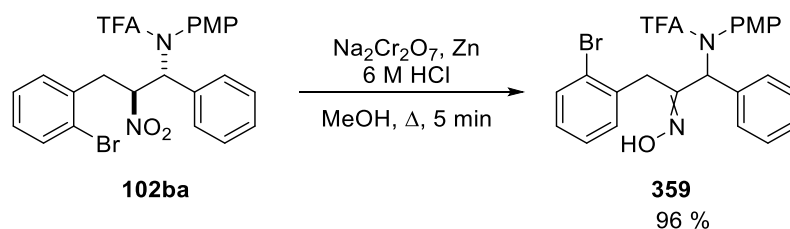
<sup>a</sup> nitroalkene number <sup>b</sup> imine number <sup>c</sup> isolated yield

## 2.2.2 Investigation of the Nef reaction of $\beta$ -nitroacetamides

### 2.2.2.1 Attempted Nef reactions of $\beta$ -nitroacetamides – Reductive

Previous attempts at Nef reaction in the Anderson group had been partly successful using chromium (II) chloride<sup>120c</sup> (**Scheme 67**).<sup>58</sup> Other attempts at the Nef reaction proved unsuccessful, giving recovered starting material or resulting in decomposition.<sup>182</sup> It was therefore decided to commence investigations with the use of CrCl<sub>2</sub>, freshly prepared via the reduction of dichromate (in this case Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>) by Zn/6 M HCl.<sup>120c</sup>

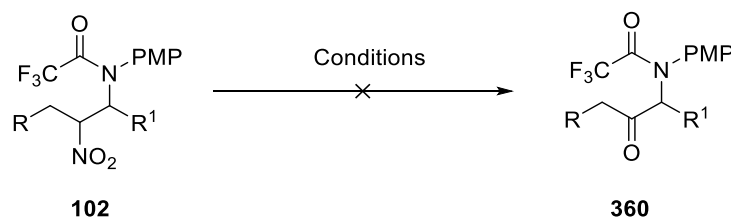
Reaction of  $\beta$ -nitroacetamide **102ba** in refluxing MeOH with  $\text{CrCl}_2$  (12 eq) proceeded to afford oxime **359** in excellent yield (**Scheme 120**).



**Scheme 120.** Nef reaction using chromium (II) chloride

Analysis of the  $^1\text{H}$  NMR spectrum showed no OH peak, and the spectrum was similar to that expected for a carbonyl. However high resolution mass spectrometry (HRMS) (calc. 521.06876, found 521.06933) suggested the formation of an oxime; this was supported by the IR spectrum, with peaks at 3414 (O-H) and 1678 ( $\text{C}=\text{N}$ ) which identify the oxime functional group. The peak for the TFA  $\text{C}=\text{O}$  bond was visible as a shoulder at 1690 – 1700  $\text{cm}^{-1}$ . Proton and carbon NMR shifts were assigned using COSY and HMQC spectra. The presence of the TFA protecting group was definitively confirmed by  $^{19}\text{F}$  NMR (- 67.7 ppm). Only one isomer of the oxime was visible by  $^1\text{H}$  NMR spectroscopy; it is likely that this is the (*E*)-isomer due to steric factors. Unfortunately as no –OH peak was present in the  $^1\text{H}$  NMR spectrum the orientation could not be assigned by NOESY correlation. Interestingly, no loss of bromide was observed under the reaction conditions, which is known to occur upon reaction of alkyl and aryl bromides with  $\text{CrCl}_2$ .<sup>120a</sup> This may occur upon more extended periods of reflux, but fortunately nitro reduction was almost instantaneous, hence only a short reaction time (5 – 30 min) was required.

It is known that reaction of nitro groups with  $\text{CrCl}_2$  may proceed fully to the imine, with hydrolysis to afford a carbonyl, or the reduction may stop at the oxime.<sup>183</sup> Doubling the equivalents of  $\text{CrCl}_2$  used (24 eq) resulted only in oxime formation and no further reduction of the oxime **359** to the imine/carbonyl (Entry 2, **Table 3**).

**Table 3.** Nef reaction of  $\beta$ -nitroacetamides using reductive conditions

Entry	102	Reagents/Conditions	Result	% Yield
1	102ba	CrCl <sub>2</sub> (12 eq), MeOH/H <sup>+</sup> , reflux	Oxime <b>359</b>	<b>359</b> (96) <sup>a</sup>
2	102ba	CrCl <sub>2</sub> (24 eq), MeOH/H <sup>+</sup> , reflux	<b>359</b>	-
3	102aa	TiCl <sub>3</sub> (4 eq), THF, 2 d, rt	No reaction	-
4	102aa	TiCl <sub>3</sub> (4 eq), THF reflux	No reaction	-
5	102aa	TiCl <sub>3</sub> (8 eq), THF, 4 d rt then reflux	No reaction	-
6	102aa	i) NaOMe, MeOH ii) TiCl <sub>3</sub> , NH <sub>4</sub> OAc	No reaction	-
7	102aa	Bu <sub>3</sub> P, PhSSPh, DCM, rt, 1 d then reflux 1 d	No reaction	-

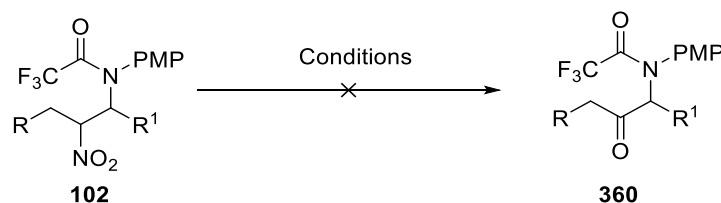
<sup>a</sup> Isolated yields <sup>b</sup> Conversion by <sup>1</sup>H NMR

Other reductive conditions were attempted on  $\beta$ -nitroacetamide **102aa**, due to its simpler synthesis directly from commercially available *trans*- $\beta$ -nitrostyrene **64a** (**Table 2**). These reactions proved less successful (**Table 3**). Unfortunately reduction of the nitro group via the McMurry Nef protocol (TiCl<sub>3</sub>, various conditions)<sup>118</sup> did not yield any product. Use of TiCl<sub>3</sub> at pH < 1 led to recovery of starting material even after long reaction times, at reflux, or with an increase of 4 to 8 eq TiCl<sub>3</sub> (Entries 3 - 5). Addition of base followed by TiCl<sub>3</sub>/NH<sub>4</sub>OAc buffer led to recovery of starting material, with a trace (< 5 %) of unidentified product (Entry 6). An alternative reductive method described by Barton<sup>121</sup> using Bu<sub>3</sub>P/PhSSPh was attempted, however this also resulted in recovery of starting material (Entry 7, **Table 3**).

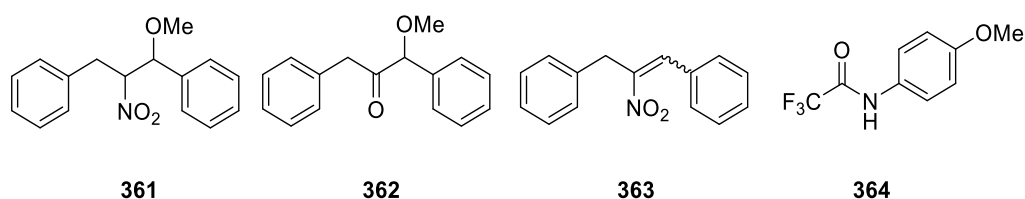
#### 2.2.2.2 Attempted Nef reactions of $\beta$ -nitroacetamides – Solvolytic, Oxidative and other methods

With an initial lack of success at the reductive Nef method, extension to the solvolytic, oxidative and other Nef reactions was the next logical step for a direct conversion to the carbonyl. The results are displayed below (**Table 4**).

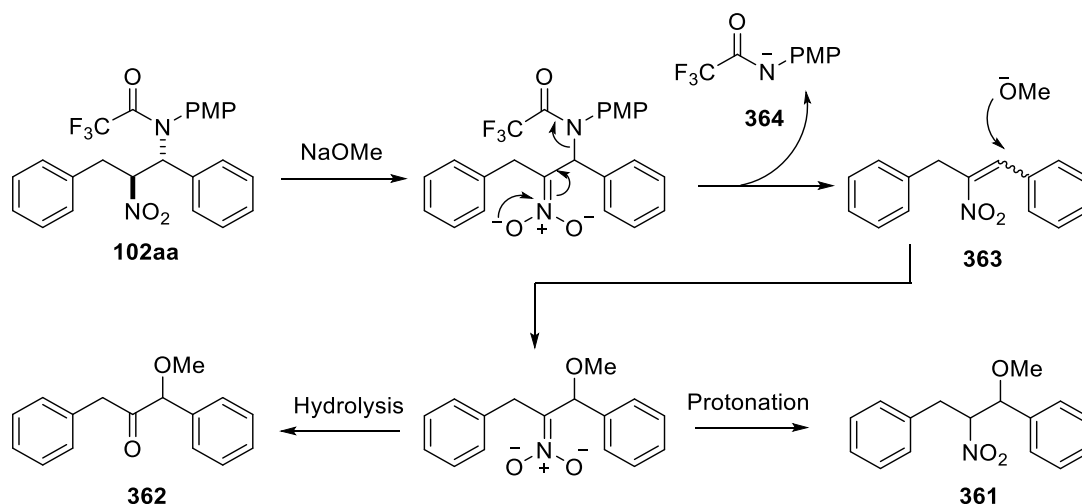


**Table 4.** Nef reaction of  $\beta$ -nitroacetamides under solvolytic, oxidative and other conditions

Entry	102	Reagents/Conditions	361:362:363 ratio	% Yield
1	102aa	i) NaOMe (1.2 eq), rt, MeOH, o/n ii) HCl work-up	0:100:0	<b>362</b> (34) <sup>a</sup> <b>364</b> (79) <sup>a</sup>
2	102aa	i) NaOMe (1.2 eq), rt, MeOH, 3.5 h ii) HCl work-up	0:0:100	<b>363</b> (56) <sup>b</sup> <b>364</b> (100) <sup>b</sup>
3	102aa	i) NaOMe (2 eq), rt, MeOH ii) H <sub>2</sub> SO <sub>4</sub> , MeOH	0:0:100	<b>363</b> (< 5) <sup>b</sup> <b>364</b> (44) <sup>a</sup>
4	102aa	i) NaOMe (2 eq), 0 °C, MeOH ii) H <sub>2</sub> SO <sub>4</sub> , MeOH	No reaction	-
5	102aa	i) NaOMe (1.2 eq), 50 °C, MeOH, 2 h ii) HCl work-up	80:0:20	<b>361</b> (53) <sup>b</sup> <b>363</b> (16) <sup>b</sup> <b>364</b> (88) <sup>b</sup>
6	102ba	i) Na <sub>2</sub> HPO <sub>4</sub> , NaOH ii) Oxone, rt, 1 d	No reaction	-
7	102aa	i) KOH, MeOH ii) conc aq KMnO <sub>4</sub> , MgSO <sub>4</sub> , MeOH, 0 °C	100:0:0	<b>361</b> (70) <sup>a</sup> <b>364</b> (100) <sup>a</sup>
8	102aa	i) NaOMe (2 eq) ii) O <sub>3</sub> , - 78 °C	-	<b>362</b> (53) <sup>a</sup> (100) <sup>b</sup>
9	102aa	NaNO <sub>2</sub> , DMF-H <sub>2</sub> O, 45 °C, 1 d	0:0:100	<b>363</b> (100) <sup>b</sup> <b>364</b> (100) <sup>b</sup>

<sup>a</sup> Isolated yields <sup>b</sup> Conversion by <sup>1</sup>H NMR**Fig. 6.** Side products resulting from elimination of **364** and subsequent reactive paths

A common characteristic of the solvolytic, oxidative and sodium nitrite mediated Nef reactions (Entries 1 – 9, **Table 4**) is deprotonation of the nitro group as the first step. Solvolytic reactions of  $\beta$ -nitroacetamide **102aa** using NaOMe to form the nitronate followed by acidic work-up (Entries 1 – 4, **Table 4**) resulted in the formation of side products and no desired carbonyl **360** was observed. In addition, Nef reactions attempted with Oxone,<sup>110a</sup> permanganate<sup>184</sup> and ozone,<sup>111a</sup> (Entries 5 – 7) and even the mild conditions of the sodium nitrite<sup>128b</sup> Nef reaction (Entry 8) all demonstrated decomposition to the same by-products. Isolation and characterisation of these decomposition products **361** – **364** (**Fig. 6**) gave an insight into the mechanistic pathways of the nitronate formed via deprotonation. The nitronate anion generated via deprotonation of **102aa** may undergo rapid elimination of the *N*-(4-methoxyphenyl)-*N*-2,2,2-trifluoroacetamide **364** to generate nitroalkene **363**. Addition of methoxide to nitroalkene **363** could generate a second nitronate anion. The  $\beta$ -methoxy nitronate anion could then undergo protonation to give  $\beta$ -methoxynitro compound **361** or hydrolysis to give  $\alpha$ -methoxyketone **362**, depending on the reaction conditions (**Scheme 121**). Further reaction to more complex by-products is also possible (e.g. aldol/Henry reactions if a combination of by-products are present in a basic environment).



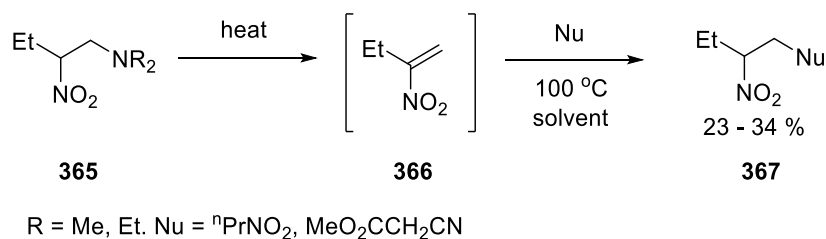
**Scheme 121.** Mechanistic pathways following elimination of the trifluoroacetamide group

The  $\text{pK}_a$  of TFA-NH-PMP is quite low ( $\sim 13$ )<sup>185</sup> compared to the nitro group ( $\sim 17$ ) (acidity in DMSO); the TFA-NH-PMP anion is stabilised due to its ability to delocalise the anion over the highly electron withdrawing TFA amide, and also into the benzene ring. Elimination to form the more stabilised anion is entropically favourable, hence elimination of **364** under basic conditions is fast at rt.

The solvolysis experiments of NaOMe followed by HCl work-up show that at rt, long reaction times are required for Michael addition of the methoxide anion into the nitrostyrene **363** (Entries 1 & 2). Quenching the reaction with H<sub>2</sub>SO<sub>4</sub> resulted in the degradation of the by-products formed (entry 3), however it would appear that the parent  $\beta$ -nitroacetamide **102aa** survives this work-up. Reaction of NaOMe (1.2 eq) at 0 °C resulted in no reaction (entry 4), presumably deprotonation is retarded at this lower temperature using NaOMe/MeOH (Reaction of DBU at this temperature or lower results in elimination, see **Table 28**). Increasing the temperature of the reaction (entry 5) to 50 °C resulted in the formation of protonated methoxy addition product **361** and some nitroalkene **363**. Not all nitroalkene has undergone addition of methoxide, also it appears that the work-up conditions are not acidic enough to cause hydrolysis of the nitronate anion. Oxidative Nef reaction using Oxone (entry 6, **Table 4**) gave no reaction. This may be due to the mildly basic reaction conditions, resulting in no deprotonation of the  $\beta$ -nitroacetamide **102ba** and hence no further reaction. The use of KMnO<sub>4</sub> (Entry 7) led to the isolation of  $\beta$ -methoxynitro compound **361** in 70 % yield. This suggests that reprotonation of the nitronate generated from addition of methoxide into the nitroalkene has occurred before addition of KMnO<sub>4</sub> as oxidation of nitronates by KMnO<sub>4</sub> is known to proceed almost instantly.<sup>109</sup> Deprotonation using NaOMe followed by oxidation with ozone resulted in the formation exclusively of  $\alpha$ -methoxyketone **362** in 53 % yield (Entry 8). This is unsurprising as ozone is a strong oxidant and is known to efficiently convert nitronate C=N bond into a carbonyl C=O bond.<sup>111a</sup> However, due to the fast elimination the oxidation occurs on the undesired nitronate produced via addition of methoxide to the nitroalkene **363**. Nef reaction via the method described by Mioskowski<sup>128b</sup> using NaNO<sub>2</sub> also proved unsuccessful. Reaction conditions are mild and the reaction is thought to proceed via a range of possible mechanistic pathways (**Scheme 70**) after initial generation of a nitronic acid **222**. Formation of this nitronic acid is thought to proceed via initial deprotonation of the nitro group by the nitrite anion to generate a nitronate.<sup>128b, 131a</sup> This would account for the elimination observed on applying this reaction to  $\beta$ -nitroacetamide **102aa**. Under the mild conditions, and in the absence of methoxide, conversion to equimolar quantities of nitroalkene **363** and trifluoroacetamide **364** was observed (Entry 9, **Table 4**).

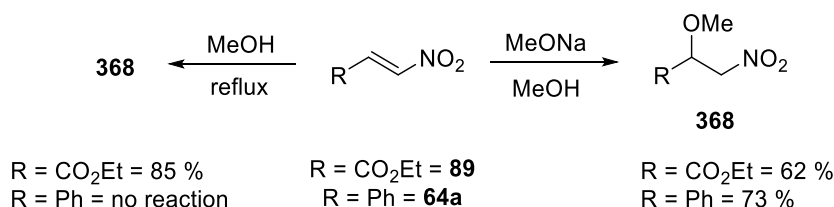
Elimination of the trifluoroacetamide **364** is favourable, due to its low pK<sub>a</sub>. However, elimination  $\beta$ -to a nitro group is known under non-basic conditions, and also for less

acidic amide<sup>12</sup> or amine<sup>186</sup> leaving groups. Elimination of the amine or its derivative can take place at high temperatures,<sup>12</sup> or a combination of high temperature and pressure,<sup>186a</sup> or via base catalysis.<sup>186c</sup> The elimination reaction has been used to generate nitroalkenes for further use in synthesis (**Scheme 121**).<sup>186b</sup>



**Scheme 121.** Elimination of amines from  $\beta$ -nitroamines to form nitroalkenes

Previous work in the Anderson group has examined the addition of alcohols and their anions to nitroalkenes. In the case of the more activated ethyl nitroacrylate **89**, addition of MeOH to the alkene was possible at reflux, with addition of MeO<sup>-</sup> possible at temperatures as low as  $-78\text{ }^\circ\text{C}$ . However, addition to *trans*- $\beta$ -nitrostyrene **64a** was less successful. Reflux in MeOH led to no incorporation, however reaction at rt with NaOMe/MeOH led to good incorporation (**Scheme 122**).<sup>66a</sup> Therefore it can be deduced that addition of MeOH to the analogous nitrostyrene **363** does not occur, rather addition of methoxide leads to the generation of products **361** and **362** (**Table 4**, **Scheme 121**).



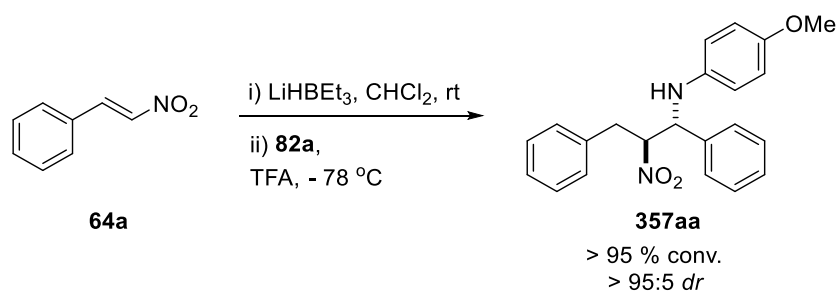
**Scheme 122.** Previous work by A. Kalogirou on the addition of alcohols to nitroalkenes

### 2.2.3 Expansion of the reaction to $\beta$ -nitroamines

The pK<sub>a</sub> of trifluoroacetamide **364** facilitated  $\beta$ -elimination from  $\beta$ -nitroacetamides **102**, hence an alternative strategy for the Nef reaction was explored. As described above,  $\beta$ -nitroamines are also known to participate in  $\beta$ -elimination reactions to form nitroalkenes,<sup>186b, c</sup> however these reactions take place under heating or base catalysis. It was thought that the higher pK<sub>a</sub> of an aniline ( $\sim 30$  vs  $\sim 13$  (**364**)) leaving group might afford the  $\beta$ -nitroamine a higher degree of stability, particularly for Nef reactions not carried out at elevated temperatures.

### 2.2.3.1 Formation of $\beta$ -nitroamine **357aa**

Formation of  $\beta$ -nitroamine **357aa** was carried out using the reductive nitro-Mannich reaction as in the preparation of  $\beta$ -nitroacetamide **102aa**, however it was not subjected to the TFA protection step. The  $\beta$ -nitroamine formed from reaction of *trans*- $\beta$ -nitrostyrene and *N*-PMP protected imine **82a** was achieved in excellent yield (> 95 % conversion by  $^1\text{H}$  NMR) and diastereoselectivity (**Scheme 123**). The *anti*- diastereoisomer was assigned by analogy with the literature.<sup>62-63, 65</sup> Crude  $\beta$ -nitroamine **357aa** was used *in situ* without further purification as these products tend to degrade on silica.<sup>55</sup>

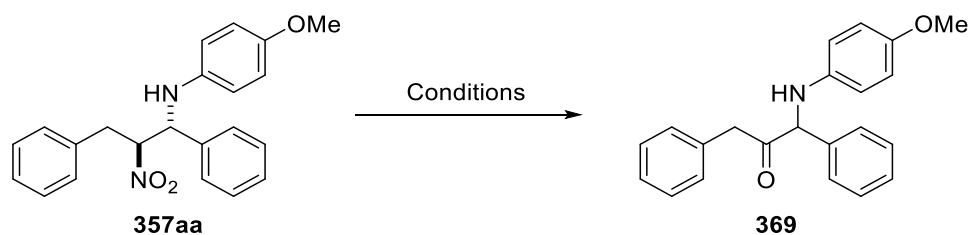


**Scheme 123.** Formation of unprotected  $\beta$ -nitroamine for investigation in the Nef reaction

### 2.2.3.2 Attempted Nef reactions of $\beta$ -nitroamine **357aa**

Subjection of  $\beta$ -nitroamine **357aa** to a variety of Nef reaction conditions analogous to those used for the  $\beta$ -nitroacetamide **102aa** was undertaken (**Table 5**).

Attempted Nef reactions of  $\beta$ -nitroamine **357aa** were more prone to decomposition and complex mixtures due to the known instability of  $\beta$ -nitroamines to retro-addition<sup>5, 22</sup> regenerating imine **82a**, and the nitroethylbenzene anion. Added complications during the Nef reaction also include possible protonation or hydrolysis/oxidation of the nitroethylbenzene anion in addition to the reaction pathways described for  $\beta$ -nitroacetamides (**Scheme 121**).

**Table 5.** Nef reactions of  $\beta$ -nitroamines

Entry	Reagents/Conditions	Result	% Yield
1	Bu <sub>3</sub> P, PhSSPh, DCM, rt, 8 h	No reaction	-
2	TiCl <sub>3</sub> (4 eq), THF, 26 h	No reaction	-
3	CrCl <sub>2</sub> , MeOH/H <sup>+</sup> , 1 h reflux	Complex mixture	-
4	i) NaOMe (2 eq), 18 h ii) H <sub>2</sub> SO <sub>4</sub> /MeOH	65:35 ( <b>363</b> :unknown product)	<b>363</b> (12 %) <sup>a</sup>
5	i) NaOMe (2 eq), MeOH ii) O <sub>3</sub> , - 78 °C	Complex mixture	-
6	CAN, NEt <sub>3</sub> , MeCN-H <sub>2</sub> O, 60 °C	Complex mixture	-
7	NaNO <sub>2</sub> , DMF-H <sub>2</sub> O	Decomposition, trace <b>363</b>	-

<sup>a</sup> Isolated yields <sup>b</sup> Conversion by <sup>1</sup>H NMR

Reaction under mild reductive conditions (Entry 1, **Table 5**) using Bu<sub>3</sub>P/PhSSPh was again unsuccessful, resulting in no reaction. Reduction by TiCl<sub>3</sub> at pH < 1 also resulted in no reaction after extended reaction times (Entry 2). This is surprising, as *N*-OMB nitroamines are known to undergo some elimination (5 %) during nitro-Mannich reaction at rt with catalytic AcOH (20 mol %) over 16 h.<sup>22</sup> However no elimination or change in *dr* was observed, suggesting this *N*-PMP  $\beta$ -nitroamine analogue **357aa** is more stable in solution at rt than others previously reported.<sup>5, 22</sup> Dry **357aa** remained stable on bench storage at rt for over 2 weeks. Reduction of **357aa** with freshly prepared CrCl<sub>2</sub> (Entry 3, **Table 5**) resulted in the formation of a complex mixture, this is likely attributable to the reaction conditions: refluxing the  $\beta$ -nitroamine in MeOH followed by addition of the acidic solution of CrCl<sub>2</sub> is likely to result in multi-pathway decomposition. Decomposition or a complex mixture was formed under all other reaction conditions attempted (Entries 5 - 7) except for solvolysis using NaOMe/H<sub>2</sub>SO<sub>4</sub> (Entry 4), which afforded mainly nitroalkene **363** and a trace quantity of an unidentified product which could not be isolated. An excess of ceric ammonium nitrate (CAN) (5 eq) and NEt<sub>3</sub> at an

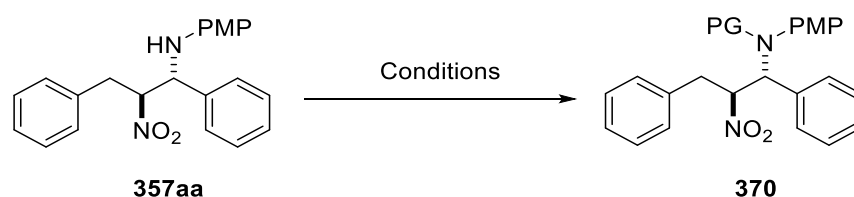
elevated temperature resulted in a complex mixture (Entry 6). The use of CAN as a reagent for the Nef reaction is known,<sup>187</sup> however it is also used to remove the *N*-PMP protecting group.<sup>21, 188</sup> Elevated temperature in the presence of a base has resulted in decomposition, and possible deprotection of the *N*-PMP amine.

These results show that Nef reaction of *N*-PMP  $\beta$ -nitroamines is complicated due to their inherent instability both to retro-addition and elimination. Further attempts towards Nef reaction of  $\beta$ -nitroamine derivatives drew on the existing Nef reactions of  $\beta$ -nitroamine derivatives by replacement of the *N*-protecting group. Many examples of the successful Nef reaction of *N*-Boc  $\beta$ -nitroamines have been described<sup>16, 88d, 132b</sup> (**Schemes 60 - 61 & 72 - 73**). This *N*-protection affords stability to the  $\beta$ -nitroamine, slowing retro-addition via delocalisation of the nitrogen lone pair into the amide. Interestingly, Liu<sup>132b</sup> described the Nef reaction of an *N*-Boc protected  $\beta$ -nitroamine, following a protecting group switch from *N*-PMP to *N*-Boc. No explanation is given for this switch, however with the results described for *N*-PMP  $\beta$ -nitroamine **357aa**, stability of these compounds appears low under most reaction conditions (**Table 5**).

## 2.2.4 Alternative strategies for the Nef reaction

### 2.2.4.1 Attempted alternative protection of $\beta$ -nitroamines

With this in mind, attempts to change the *N*-protecting group were made. Primarily, *N*-Boc or *N*-benzyl protection of the *N*-PMP protected  $\beta$ -nitroamine **357aa** was attempted (**Table 6**).



**Table 6.** Attempted alternative protection of  $\beta$ -nitroamines

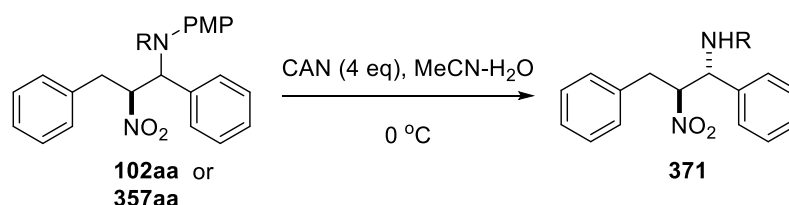
Entry	PG	Conditions	Result
1	Boc	Boc <sub>2</sub> O, DMAP, Et <sub>3</sub> N, THF, reflux, 1 h	Degradation
2	Bn	BnBr, K <sub>2</sub> CO <sub>3</sub> , DMF	SM <sup>a</sup>

<sup>a</sup>Some degradation observed

Degradation occurred on treatment of **357aa** under the conditions attempted (Entry 1, **Table 6**), presumably due to the instability of the molecule to base, and high temperature. Attempted benzylation was also unsuccessful under mild alkylation conditions (Entry 2). It would appear that under these mild conditions,  $\beta$ -nitroamines do not undergo elimination of *p*-anisidine to give nitroalkene **363**, affording mainly recovered starting material with traces of retro-addition products.

#### 2.2.4.2 Attempted removal of the *N*-PMP protecting group

Removal of the *N*-PMP protecting group of both the  $\beta$ -nitroacetamide **102aa** and  $\beta$ -nitroamine **357aa** was attempted using CAN (4 eq).<sup>21, 58, 188</sup> It was found that no reaction occurred on treatment of  $\beta$ -nitroacetamide **102aa**; a complex mixture was obtained from reaction of  $\beta$ -nitroamine **357aa** (**Table 7**).

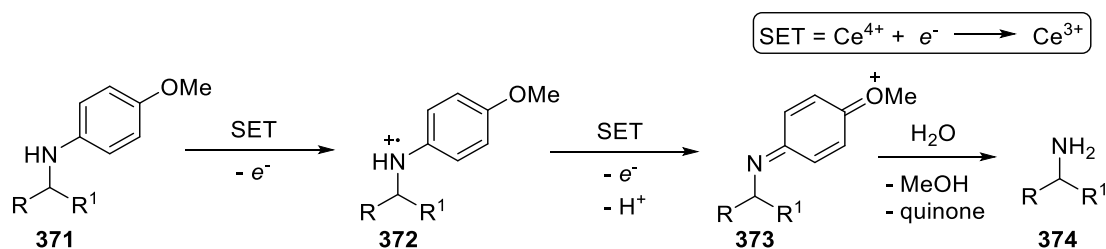


**Table 7.** Attempted removal of the *N*-PMP protecting group

Entry	R	Time	Result
1	COCF <sub>3</sub> ( <b>102aa</b> )	4 h	No reaction
2	H ( <b>357aa</b> )	2 h	Complex mixture

The mechanism of CAN deprotection is thought to occur via initial SET from the nitrogen lone pair to the Ce<sup>4+</sup> ion leading to the more stable Ce<sup>3+</sup> ion and a radical cationic nitrogen species **372**. A further SET from radical cation **372** results in the formation of Schiff base **373** via stabilisation from the oxygen lone pair on the PMP ring. Hydrolysis of this Schiff base leads to the generation of amine **374** and quinone (**Scheme 124**).<sup>189</sup> Reaction of  $\beta$ -nitroacetamide **102aa** may have stalled due to lack of lone pair availability on the amide nitrogen, which undergoes amide resonance stabilisation (however *N*-PMP deprotection of less electron-withdrawn amides is known<sup>188</sup>).

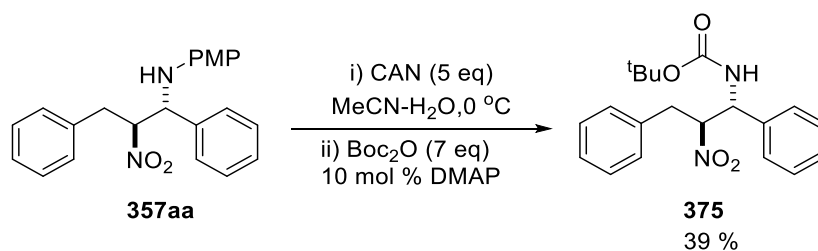




**Scheme 124.** Mechanism of *N*-PMP deprotection using CAN

As it has been shown to be stable at rt for long periods in acidic media (*vide supra*),  $\beta$ -nitroamine **102aa** may not undergo decomposition primarily via retro-addition. However competing SET pathways may exist with the nitro group, resulting in a myriad of pathways for the molecule to take, including a possible Nef reaction.<sup>187</sup>

Deprotection of *N*-PMP  $\beta$ -nitroamine **357aa** by CAN followed by addition of  $\text{Boc}_2\text{O}$  and DMAP, trapped the intermediate primary amine as *N*-Boc protected  $\beta$ -nitroamine **375** as part of previous work in this group (**Scheme 125**).<sup>190</sup>



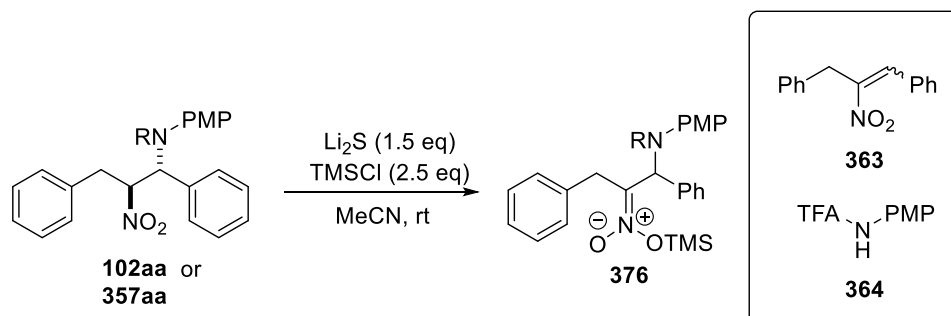
**Scheme 125.** *N*-PMP to *N*-Boc swap by P. Koovits

The primary amine intermediate **374** may be unstable to work-up conditions, hence requiring *in situ* Boc-protection for isolation. Whilst it is possible that this strategy of *N*-PMP deprotection-*N*-Boc protection may yield  $\beta$ -nitroamines more amenable to the Nef reaction, this extra manipulation is wasteful and time-consuming. In addition, *N*-Boc  $\beta$ -nitroamines are produced directly via the nitro-Mannich reaction by other groups (See section 1.1). Reaction of *N*-PMP imines followed by a protecting group swap of the product  $\beta$ -nitroamines would be redundant in light of the simpler direct reactions, hence the Nef reaction of products **375** was not investigated.

#### 2.2.4.3 Attempted Nef reaction of *O*-silyl nitronates

It is known that CAN can also reduce silyl nitronates **376** to ketones,<sup>187</sup> and it was wondered whether silyl protection may afford some stability to the nitronate. The formation of silyl nitronates<sup>191</sup> was attempted for both  $\beta$ -nitroacetamide **102aa** and  $\beta$ -

nitroamine **357aa** under weakly acidic conditions, however no silyl nitronates **376** were isolated. Instead part conversion of the starting materials to the nitroalkene **363** was observed (Entries 1 & 2, **Table 8**).

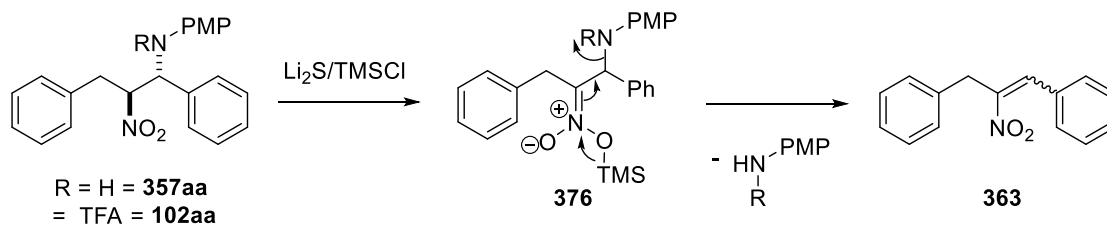


**Table 8.** Attempted formation of silyl nitronates

Entry	R	Time	SM:363 ratio	% Yield <sup>a</sup>
1	COCF <sub>3</sub> ( <b>102aa</b> )	18 h	55:45	<b>102aa</b> (30) <b>363</b> (20) <b>364</b> (70)
2	H ( <b>357a</b> )	6-8 h	70:30	<b>357aa</b> (70) <b>363</b> (30)

<sup>a</sup>Conversion by <sup>1</sup>H NMR

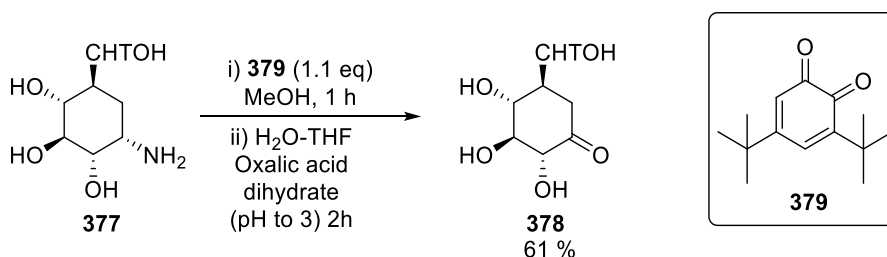
Reaction of β-nitroacetamide **102aa** resulted in a 70 % conversion to trifluoroacetamide **364**, however crude isolation of the nitroalkene **363** was lower (Entry 1, **Table 8**). The reaction of β-nitroamine **357aa** was run for a shorter time, resulting in a lower conversion (elimination to give nitroalkene – 30 % by <sup>1</sup>H NMR). This may also be partly due to the higher pK<sub>a</sub> of *p*-anisidine (*c.f.* **364**), and a lower rate of elimination. From earlier results (Entries 3-5, **Table 3** & Entry 2, **Table 5**) it was observed that under acidic conditions (pH < 1) no elimination is observed for either β-nitroacetamide **102aa** or β-nitroamine **357aa** after 2 days or under reflux. It is hypothesised that formation of silyl nitronate **376** occurs, but is followed by subsequent collapse of the silyl nitronate species in an elimination step, generating nitroalkene **363** (**Scheme 126**). The low yield of nitroalkene **363** compared with its equimolar trifluoroacetamide partner **364** seen in many examples may be due to polymerisation under the reaction conditions.



**Scheme 126.** Proposed elimination from intermediate *O*-silyl nitronate **376**

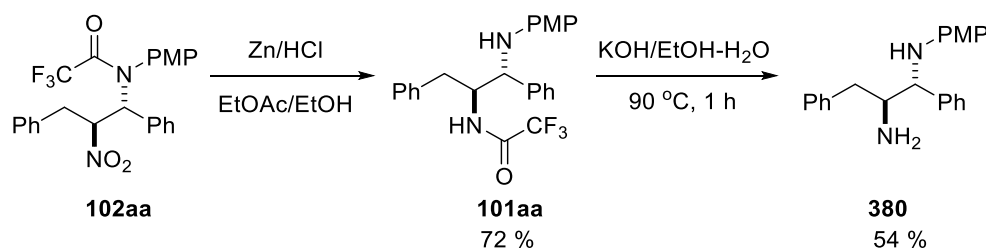
#### 2.2.4.4 Attempted Nef reaction via reduction to a 1,2-diamine

A report by Floss<sup>192</sup> detailed the oxidation of amine **377** by 3,5-di-*tert*-butyl-1,2-benzoquinone (**379**), followed by hydrolysis affording ketone **378** in good yield (**Scheme 127**).



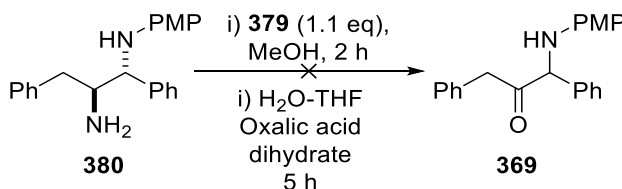
**Scheme 127.** Oxidation of a primary amine to a ketone using 3,5-di-*tert*-butyl-1,2-benzoquinone

Reduction of  $\beta$ -nitroamines and  $\beta$ -nitroacetamides to 1,2-diamines and their derivatives is well-documented (See section 1.2). Within this group, the reduction of  $\beta$ -nitroamines to 1,2-diamines using  $\text{SmI}_2$ <sup>5, 22</sup> or  $\text{Al}(\text{Hg})$ <sup>14</sup> and  $\beta$ -nitroacetamides to orthogonally protected 1,2-aminoacetamides by  $\text{Zn}/\text{Acid}$ <sup>58, 62, 65, 82c</sup> is well documented. The chosen strategy for reduction of  $\beta$ -nitroacetamide **102aa** was the  $\text{Zn}/\text{HCl}$  method described previously (**Scheme 32**), as it is known that reduction can occur with conservation of aryl-bromide functionality. This would be necessary for the formation of heterocycles **351** (See **Scheme 113**). Reduction of  $\beta$ -nitroacetamide **102aa** was carried out to afford  $\beta$ -aminoacetamide **101aa** in good yield (**Scheme 128**). Deprotection of the trifluoroacetamide was then performed to give crude 1,2-diamine **380** in 54 % yield, which was used without further purification as 1,2-diamines are known to react with carbon dioxide.<sup>5</sup>



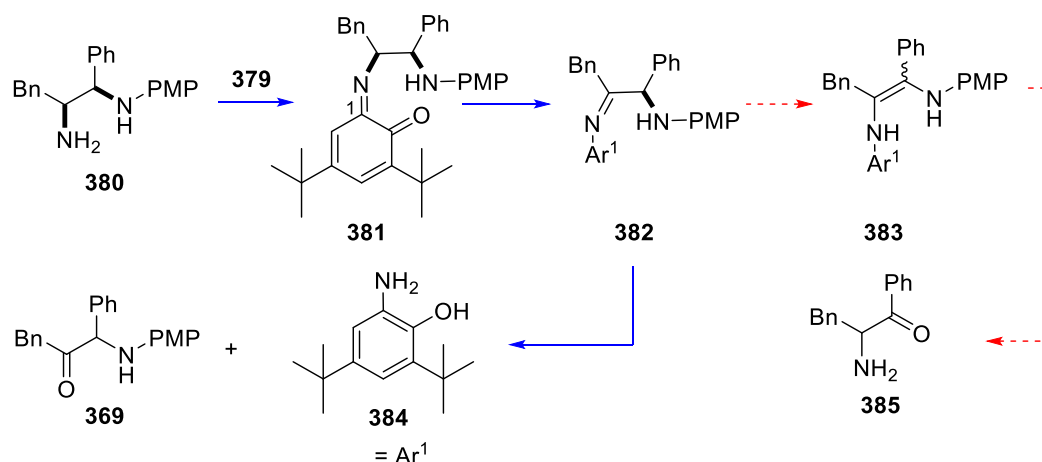
**Scheme 128.** Reduction of **102aa** to the corresponding 1,2-diamine

Subjection of the vicinal primary-secondary diamine **380** to the reaction conditions described by Floss;<sup>192</sup> oxidation using 3,5-di-*tert*-butyl-1,2-benzoquinone (**379**) followed by acidification of the reaction to pH 2-3 by oxalic acid hydrate (**Scheme 129**) resulted in the formation of a complex mixture.



**Scheme 129.** Attempted oxidation of **380** to a ketone **369**

It is unclear how much steric bias the *N*-PMP protecting group affords the secondary amine towards the bulky quinone **379**, however the delocalisation of the lone pair across the benzene ring should make this amine less nucleophilic. Thus it would be expected for attack of the primary amine to be more favourable. The oxidation mechanism is believed to proceed via initial condensation of the amine with a carbonyl on **379** followed by prototypic rearrangement to afford the corresponding Schiff base **382** which undergoes hydrolysis after acidification of the reaction mixture to afford the carbonyl **369** (**Scheme 130**).<sup>193</sup> Formation of the initial Schiff base occurs only at C-1 and no conjugate addition occurs due to the presence of the two bulky *t*-butyl groups at C-3 and C-5. It is possible that keto-enol tautomerisation may occur from **382** leading to an en-di-amine **383**. Hydrolysis of either the primary amine to afford **369** could then occur or hydrolysis at the secondary amine could lead to ketone formation at the more stable benzylic position affording **385**, leading to a mixture of products. Further reactions may also occur from these products, accounting for the complex mixture (**Scheme 130**).



**Scheme 130.** Mechanism of **379**-mediated oxidative hydrolysis of an amine

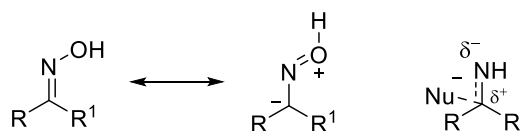
The lack of success of Nef reactions of  $\beta$ -nitroacetamides **102** and  $\beta$ -nitroamines **357a** led to abandonment of this research area in favour of a greater focus on further reactions of the oxime **359**, the only successful Nef reaction of  $\beta$ -nitroacetamide **102ba**.

## 2.2.5 Further reactions of the Oxime

### 2.2.5.1 Attempted hydrolysis

The oxime functional group is known to be a common intermediate in the reductive Nef reaction of nitro groups with several reducing agents.<sup>72d, 118, 121b</sup> It is commonly used as a ‘protecting group’ for carbonyls,<sup>194</sup> and thus it was expected that its removal would be trivial.

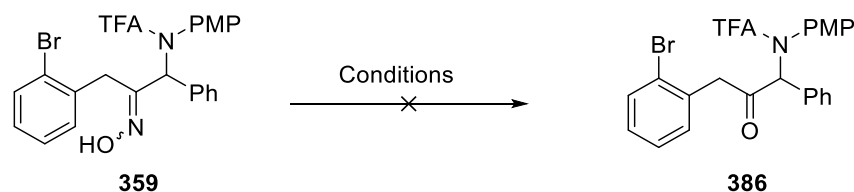
A range of methods for de-oximation are known, and similarly to the Nef reaction these fall into categories such as hydrolytic,<sup>195</sup> oxidative,<sup>196</sup> reductive<sup>121b</sup> and transoximation.<sup>197</sup> The cleavage of oximes is difficult due to their hydrolytic stability. Delocalisation over the C-N-O system leads to a higher degree of electron density at the carbon atom, making nucleophilic addition to the C=N bond more difficult, compared to similar C=N bonds such as those of imines (**Fig. 7**).<sup>198</sup>



**Fig. 7.** Hydrolytic stability of oximes *c.f.* imines

The use of harsh acidic conditions is usually required for the hydrolytic cleavage of oximes to their parent carbonyl, but this is incompatible with multiple functional groups

and may lead to undesired Beckmann rearrangement.<sup>199</sup> The transformation of oximes into less stable species (e.g. imines via reduction of the N-O bond) mean that oxidative (e.g. oxidative cleavage of the C=N bond) and reductive techniques do not require the use of strong acids.<sup>195</sup> With this information in hand, a small range of different methodologies were attempted for deoxygenation (**Table 9**).



**Table 9.** Attempted hydrolysis of oxime **359**

Entry	Reagents/conditions	Result
1	MnO <sub>2</sub> , hexanes rt, 1 d	RSM ( <b>359</b> )
2	CuCl <sub>2</sub> .2H <sub>2</sub> O, MeCN:H <sub>2</sub> O (4:1) reflux, 3 d	Decomposition
3	O <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> , - 78 °C, 5 h	RSM ( <b>359</b> )
4	CrCl <sub>2</sub> (12 eq), MeOH/H <sup>+</sup> , reflux	RSM ( <b>359</b> )

Oxidative cleavage of **359** was attempted via reaction with activated MnO<sub>2</sub> (Entry 1, **Table 9**),<sup>196a</sup> however no reaction was observed. Hydrolytic cleavage of **359** via a mild method using CuCl<sub>2</sub>.H<sub>2</sub>O described by Shi was attempted.<sup>195</sup> The reaction was followed by TLC for 3 days, with the oxime **359** remaining present during this time, however on work-up of the reaction, a complex mixture was observed (Entry 2). The use of CuCl<sub>2</sub>.H<sub>2</sub>O is thought to drive the reaction to completion by formation of a favourable Cu-bound hydroxylamine compound (Cu(NH<sub>2</sub>OH)Cl<sub>2</sub>).<sup>195</sup> It is possible that under the reaction conditions, coordination of the Cu<sup>2+</sup> species to the oxime may facilitate Beckmann rearrangement, leading to a mixture of products.

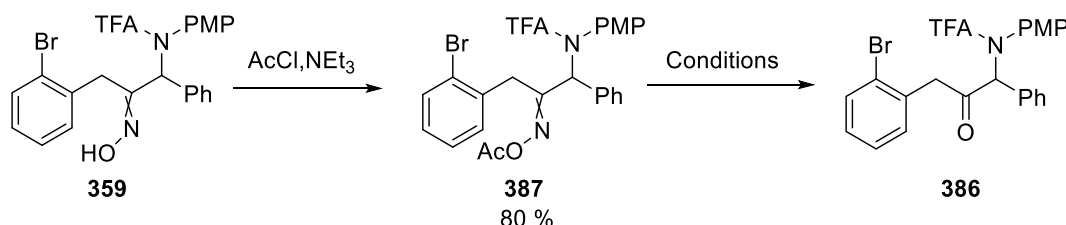
Nef reaction of the corresponding nitronates of β-nitroacetamide **102aa** (Entry 8, **Table 4**) and β-nitroamine **357aa** (Entry 5, **Table 5**) by ozone was previously attempted, but proved unsuccessful. The C=N bond cleavage of oximes by ozone has been reported, and oximes do not present the same problem of elimination that plagued the aforementioned compounds. It was thought that subjection of **359** to ozone might prove a clean and successful procedure for deoxygenation. Saturation of a solution of **359** in CH<sub>2</sub>Cl<sub>2</sub> with O<sub>3</sub> at - 78 °C proved unsuccessful, with recovery of starting material only. In hindsight this

was not surprising as previous ozonation of oximes has proved difficult, with long reaction times required (8 -10 h) for good yield (85 %).<sup>196b</sup> However the lack of any other product as seen by <sup>1</sup>H NMR of the crude reaction material, meant that subjection of **359** to ozone for longer periods of time would be unlikely to generate product **386**.

The reduction of  $\beta$ -nitroacetamide **102ba** by freshly prepared CrCl<sub>2</sub> proved successful in the isolation of oxime **359**, however doubling the equivalents did not lead to reduction of the oxime further to the imine (Entries 1 & 2, **Table 3**). Subjection of the isolated oxime to the initial reaction conditions described for nitro compounds was unsuccessful, resulting in recovered starting material only (Entry 4, **Table 9**). It would appear the intermediate oxime possesses a higher degree of stability to reduction by SET processes than the parent nitro compound. Indeed the lack of success so far suggested that oxime **359** may be highly stable, and other efforts were made to render it more susceptible to deoxygenation.

#### 2.2.5.2 Oxime acetylation and further attempts at hydrolysis

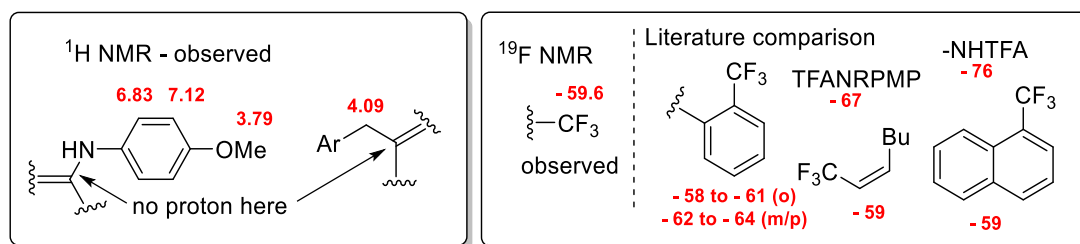
In order to reduce the hydrolytic stability of the oxime, it was acetylated successfully, with isolation of *N*-acetoxy oxime **387** in 80 % yield (**Table 10**). With the electron withdrawing effect of the acetate the electron density on the C=N carbon should be reduced, and the oxime more amenable to hydrolysis.



**Table 10.** Attempted hydrolysis of *N*-acetoxy oxime **387**

Entry	Reagents/conditions	Result
1	i) AcCl, NEt <sub>3</sub> , (80 %) ii) Fe/AcOH, Ac <sub>2</sub> O	Unidentified product, no <b>386</b>
2	i) AcCl, NEt <sub>3</sub> , (80 %) ii) Fe/AcOH	Unidentified product, no <b>386</b>
3	Mo(CO) <sub>6</sub> , EtOH-H <sub>2</sub> O, reflux, 30 h	Complex mixture ( <b>359</b> )

Reduction of oxime acetates (or pivalates)<sup>200</sup> by Fe(0)/AcOH proceeds via reduction of the N-O bond to afford an imine, which can be hydrolysed. Alternatively tautomerisation to an enamine and trapping in the presence of Ac<sub>2</sub>O can be performed to capture the enamide. It was envisaged based on this mechanism that reduction of *N*-acetoxy oxime **387** to the corresponding imine would result in the formation of carbonyl **386** after hydrolysis *in situ*. Alternatively, trapping of the enamide with Ac<sub>2</sub>O could lead to hydrolysis after deprotection of the acetate group. Both reactions were attempted, with the same result; the same unidentified product was formed (Entries 1 & 2, **Table 10**). Attempts at identification of the product by mass spectrometry (CI<sup>+</sup>) has been unforthcoming, the fragments do not appear to match any conceivable molecule, expected or rearranged. However it can be inferred from isotopic distribution peaks (<sup>79</sup>Br:<sup>81</sup>Br 50:50, for peaks 515:517; 488:490, and 468:470) that a bromine atom is present in the molecule. Other information that can identify fragments of the molecule present include the presence of -NHPMP (PMP peaks in <sup>1</sup>H NMR (**Fig. 8**). The OMe peak at  $\delta$  3.79 ppm (3H, s) is present, and the two peaks at  $\delta$  6.83 ppm (2H, dm,  $J$  = 9.0) and 7.12 ppm (2H, dm,  $J$  = 8.9) are characteristic of a non-TFA protected *N*-PMP structure; TFA protection renders each proton inequivalent. Information that can be gleaned from the <sup>1</sup>H NMR spectrum include a benzylic CH<sub>2</sub> peak at  $\delta$  4.09 ppm, with no adjacent protons (**Fig. 7**); a broad singlet at  $\delta$  4.19 ppm could indicate the presence of an NH<sub>2</sub>, and there are 9 aromatic protons in addition to those from the PMP group.



**Fig. 8.** <sup>1</sup>H NMR data used in the identification of features of the unidentified product

Perhaps the most interesting result is the shift of the fluorine environment of the CF<sub>3</sub> group by <sup>19</sup>F NMR from  $\delta$  - 67.4 (**387**) to - 59.6 ppm, which shows a change of environment. From previous work by A. Noble,<sup>201</sup> *o*-trifluoromethyl type compounds (where this molecule is part of a  $\beta$ -nitroacetamide/ $\beta$ -nitroamine/tetrahydroquinoline) exhibit a <sup>19</sup>F NMR range of  $\delta$  - 58 to - 61 ppm. The most similar values around  $\delta$  - 59 ppm were exhibited by  $\beta$ -nitroamines formed from an *o*-CF<sub>3</sub> substituted aryl imine. Values observed in this work<sup>202</sup> of approximately  $\delta$  - 67 ppm for PMP-trifluoroacetamides

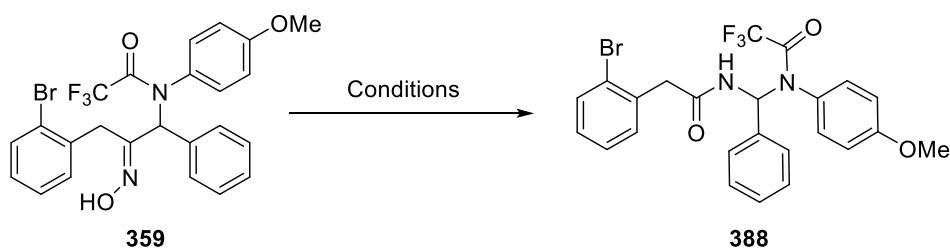


and  $\delta$  - 76 ppm for non-PMP substituted trifluoroacetamides are far from the observed value of  $\delta$  - 59.6 ppm; the  $\text{CF}_3$  group is not in either of these environments. Comparison of the literature<sup>203</sup> shows similar values of  $\delta$  - 59 ppm for 1- $\text{CF}_3$  naphthalene or a cis-alkene. Proximate alkyl groups can have a deshielding effect due to interaction of the van der Waals radius of the alkyl group with the electrons on fluorine, causing the nucleus to respond to the magnetic force as though it had a lower electron density.<sup>203</sup> It is not clear which environment the  $\text{CF}_3$  group is in; interaction of a proximate alkyl group may help explain the large change in  $^{19}\text{F}$  NMR ppm value, or the  $\text{CF}_3$  group may be in a very different environment via an unexpected rearrangement. Usually  $^{13}\text{C}$  NMR would be used to help assign the TFA group, however with only 5 mg of compound the  $^{13}\text{C}$  NMR was difficult to assign as the signals were very weak. Peaks for the benzylic  $\text{CH}_2$  ( $\delta$  33.7 ppm) OMe ( $\delta$  55.5 ppm) and aromatic/PMP carbons were clearly identified. Unfortunately no X-ray crystallography data was obtained, and the structure of the unidentified compound could not be ascertained. Reaction of the *N*-acetoxy oxime **387** with  $\text{Mo}(\text{CO})_6$  was also attempted,<sup>204</sup> leading to a complex mixture, containing deacetylated oxime **359** as the major product (Entry 3, **Table 10**).

A range of other techniques for the deoxygenation of oxime **359** or *O*-acetoxy oxime **387** could be attempted, however due to the lack of success it was decided to attempt a range of different transformations of the oxime.

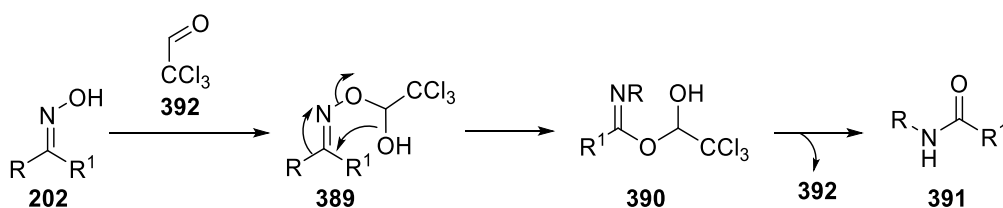
#### 2.2.5.3 Attempted Beckmann rearrangement

The Beckmann rearrangement is an important reaction for the formation of amides from oximes. Beckmann rearrangement was attempted using oxime **359** (**Table 11**). Activation of **359** via *in situ* mesylation followed by heating in the presence of basic  $\text{Al}_2\text{O}_3$ <sup>205</sup> resulted in no Beckmann rearrangement (Entry 1, **Table 11**). Even under high temperature, rearrangement did not occur, so other conditions were attempted.

**Table 11.** Attempted Beckmann rearrangement of oxime **359**

Entry	Conditions	Result
1	i) Py, MsCl, CHCl <sub>3</sub> 0 °C (43 %) ii) CHCl <sub>3</sub> , Al <sub>2</sub> O <sub>3</sub> 120 °C	No reaction
2	i) Chloral hydrate, 10 torr 130 °C ii) 760 torr 130 °C	No reaction
3	TFA, reflux, 3 h	Decomposition

Lewis acidic chloral **392** is known to promote the Beckmann rearrangement under mild conditions,<sup>206</sup> and can be generated from its hydrate by heating at low pressure (Entry 2). However the reaction proved unsuccessful and no product was observed, only recovered starting material. It may be that removal of a mole of water from chloral hydrate did not occur efficiently. Alternatively, the oxime may be too hydrolytically stable to the nucleophilic attack of the hydroxyl group of the chloral adduct **389** on the C=N bond (Scheme 131). In either case, isolation of the oxime would occur.

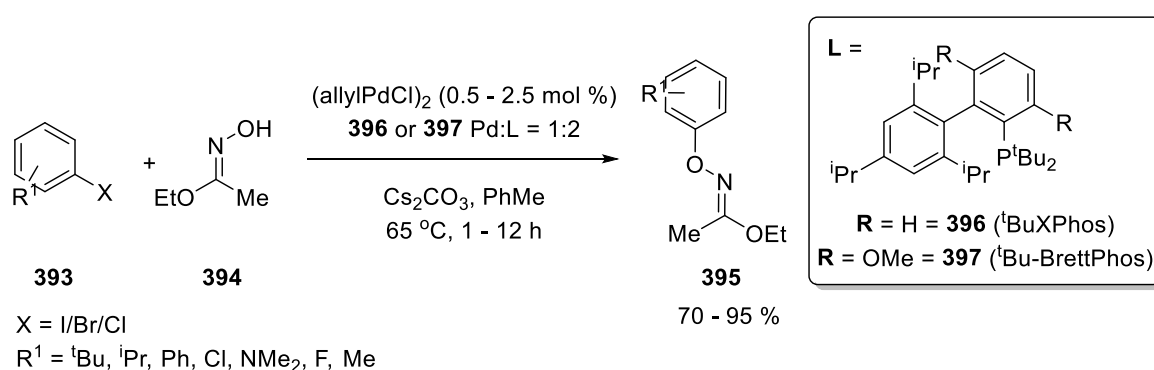
**Scheme 131.** Beckmann rearrangement using chloral

Due to the lack of reaction of the oxime, harsher conditions were attempted. Refluxing oxime **359** in TFA for 3 hours led to degradation, isolation of imine **82a**, TFA-NH-PMP **364** and an unidentified product. It would appear that these conditions may result in the acid-decomposition of the oxime, regenerating the imine and possibly resulting in the formation of a nitrile, which may undergo further reaction. Nitrile formation is known as an alternative pathway in the Beckmann rearrangement.<sup>199</sup> It is also unclear whether any

Beckmann product of type **388** would be isolable, in particular under such acidic conditions, as the molecule contains a tri-protected aminal-type functional group, which could undergo hydrolysis to give TFA-NH-PMP **364**, benzaldehyde and 2-bromophenylacetamide.

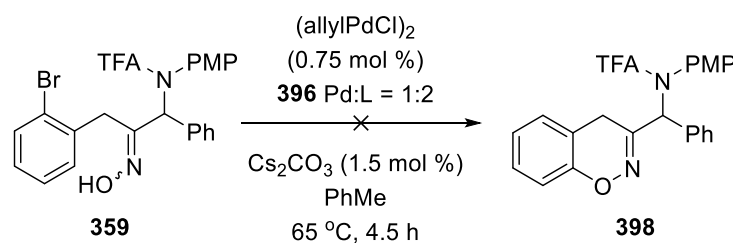
#### 2.2.5.4 Intramolecular coupling of oxime **359**

The presence of the aryl bromide in the oxime led us to ponder whether it may be possible to conduct a coupling reaction with the oxime –OH. Intermolecular coupling of these oximes with aryl halides is known using Pd (0)-catalysis such as the (allylPdCl)<sub>2</sub>-catalysed addition of ethyl acetate oxime **394** to aryl halides **393** described by Buchwald (Scheme 132).<sup>207</sup>



**Scheme 132.** Oxime coupling with aryl halides using Pd(0)

Intramolecular cyclisation of oxime **359** was attempted under the conditions described<sup>207</sup> using 0.75 mol % (allylPdCl)<sub>2</sub>, 1.5 mol % <sup>t</sup>BuXPhos **397** (more effective for *o*-substituted bromides) and 1.5 mol % Cs<sub>2</sub>CO<sub>3</sub> (Scheme 133). Following the reaction by TLC showed the presence of many spots indicating a complex mixture, which was confirmed on work up by <sup>1</sup>H NMR.



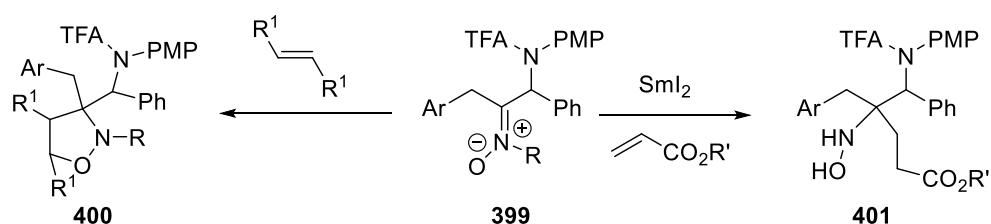
**Scheme 133.** Attempted intramolecular oxime-aryl bromide coupling of **359**

It was not definite that the oxime **359** was the (*E*)-configuration as shown, however if the oxime were the (*Z*)-geometry, *o*-cyclisation would not occur. It was not possible to tell

whether insertion of palladium into the C-Br bond has taken place due to the complex mixture. It is possible that insertion occurs and is not followed by complexation of the oxime; alternatively the oxime may form a stable complex that does not undergo reductive elimination under these conditions.

### 2.2.5.5 Formation of nitrones

The formation of nitrones **399** from oxime **359** would be of interest as nitrones participate in cycloadditions,<sup>208</sup> and undergo SmI<sub>2</sub>-mediated coupling reactions with Michael acceptors<sup>209</sup> (**Scheme 134**).

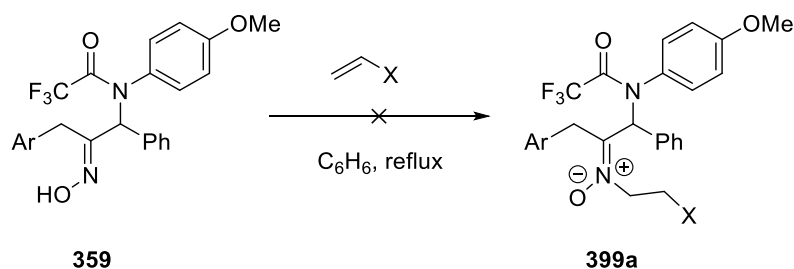


**Scheme 134.** Possible reactions of nitrones generated from oxime **359**

Synthesis from oximes is one of the simplest and easiest ways to generate nitrones.<sup>74</sup> In contrast to the formation of nitrones from some other functional groups (e.g. amines, hydroxylamines), synthesis from oximes requires only alkylation of the nitrogen atom, as the oxime is at the correct oxidation state. Methods for alkylation include the use of direct alkylating agents (e.g. MeI) or addition to activated unsaturated bonds (e.g. a Michael acceptor).<sup>74</sup>

#### 2.2.5.5.1 The Grigg nitrone formation

The *N*-alkylation of oximes via Michael addition to an electron poor alkene is known as the Grigg reaction.<sup>210</sup> Problems with the Grigg reaction include the subsequent cycloaddition reaction of the nitrones formed in inter- or intramolecular cycloaddition reaction in the presence of dipolarophiles leading to the isolation of mainly cycloaddition products. Reaction of oximes with Michael acceptors mediated by Lewis acids was reported by Kanemasa<sup>211</sup> for the formation of nitrones, Michael addition is facilitated and addition of a Lewis acid also slows the cycloaddition process. This formed the starting point for investigations into the alkylation of **359**.

**Table 12.** Grigg alkylation of oxime **359** by Michael acceptors for nitronium generation

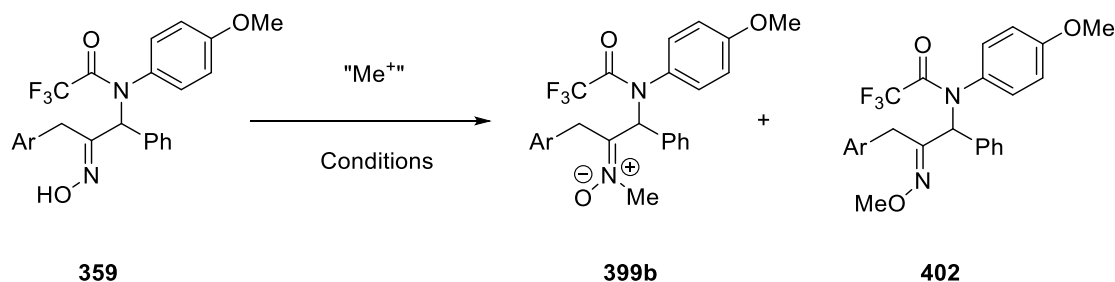
Entry	CH <sub>2</sub> CH <sub>2</sub> X eq (X)	ZnI <sub>2</sub> /BF <sub>3</sub> OEt <sub>2</sub> eq	time	Result
1	1.5 (CN)	0	6 h	SM
2	1.5 (CN)	0.5/0.5	6 h	SM
3	1.5 (CO <sub>2</sub> Me)	0.5/0.5	o/n	Complex mixture

Reaction of oxime **359** with acrylonitrile was first attempted in the absence of Lewis acid (Entry 1, **Table 12**) however this resulted in recovered starting material **359**. A 1:1 mixture of Lewis acids ZnI<sub>2</sub>/BF<sub>3</sub>.OEt<sub>2</sub> (total 1 eq) was reported by Kanemasa<sup>211</sup> to provide optimum conditions for the nitronium formation however this also resulted in no reaction after reflux in benzene for 6 h (Entry 2). Substitution of acrylonitrile with methyl acrylate was attempted in the presence of ZnI<sub>2</sub>/BF<sub>3</sub>OEt<sub>2</sub> leading to the isolation of a complex mixture by <sup>1</sup>H NMR (Entry 3). The Grigg reaction was reported by Kanemasa to be sluggish for ketoximes, but made possible using forcing conditions such as refluxing in benzene. It appears that reaction of the oxime with acrylonitrile is unfavourable. In contrast, reaction of the oxime with methyl acrylate may lead to formation of the nitronium followed by cycloaddition pathways or decomposition under the forcing conditions used. It was previously shown that decomposition occurs under acidic conditions at reflux (Entry 3, **Table 11**); Lewis acids ZnI<sub>2</sub> or BF<sub>3</sub>.OEt<sub>2</sub> could cause the same decomposition to occur.

#### 2.2.5.5.2 Methylation of **359**

Due to the lack of success with the Grigg reaction, a variety of attempts at simple *N*-alkylation of the oxime **359** were attempted. However, due to the presence of both the *N*- and *O*-alkylation sites of oximes, problems were encountered with selective alkylation. In all cases attempted, trace amounts of the suspected nitronium **399b** were visible in the

crude  $^1\text{H}$  NMR spectra. The major side reaction was the competing *O*-alkylation product tentatively identified also by its presence in the crude  $^1\text{H}$  NMR spectra.



**Table 13.** Nitron formation by *N*-methylation of oxime **359**

Entry	Base (eq)	"Me <sup>+</sup> " (eq)	Solvent/ Conds	Result <sup>a</sup>
1	<sup>t</sup> BuOK (1.2)	MeI (10)	MeCN, rt then reflux o/n	Ratio: <b>359</b> : <b>399b</b> : <b>402</b> = 65:5:30
2	KH (1.5)	MeI (10)	MeCN, rt to reflux o/n	Complex Mixture - trace of <b>399b</b>
3	-	Me <sub>3</sub> OBf <sub>4</sub> (1.1)	DCM, rt 4 d	Complex mixture –trace of <b>399b</b>

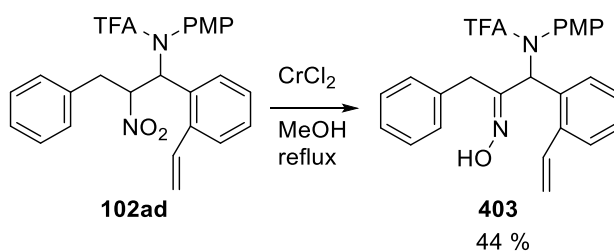
<sup>a</sup>**399b** and **402** tentatively assigned from TLC, Mass Spec and  $^1\text{H}$  NMR data

Work by L'abbé<sup>212</sup> had suggested that the nature of the alkylating reagent was essential to the correct alkylation product formed. Their work showed that alkylation with diazomethane resulted in preferential *O*-alkylation. Formation of the potassium salt of the oxime followed by addition of softer methyl iodide, gave a higher ratio of *N*-alkylation. Formation of the potassium salt of oxime **359** using <sup>t</sup>BuOK followed by addition of a large excess of MeI resulted in a mixture of recovered starting material, and both alkylation isomers **399b** and **402** (Entry 1, **Table 13**). Only a trace of *N*-alkylation was observed. Formation of the potassium salt of oxime **359** by KH under the same conditions resulted in a complex mixture, with only a trace amount of the suspected nitron **399b** visible (Entry 2). Reaction under acidic conditions (Me<sub>3</sub>OBf<sub>4</sub>) also gave a complex mixture including trace **399b**. The presence of **399b** was indicated by  $^1\text{H}$  NMR - showing benzylic doublets at  $\delta$  3.54, 4.52 ppm ( $J$  = 16.4) and the presence of an N-Me singlet peak at  $\delta$  3.91 ppm (PMP-OMe peak at  $\delta$  3.68 ppm). Ether **402** has more shielded

benzylic protons at  $\delta$  3.25, 4.11 ppm ( $J = 16.2$ ) and an OMe peak at  $\delta$  4.04 ppm (PMP-OMe peak at  $\delta$  3.71 ppm). The close proximity of the NMe and OMe peaks are difficult to differentiate, however the electron-withdrawing effect of the nitrone C=N bond would be likely to deshield the protons in the benzylic position to a greater extent than the oxime ester. In addition, **402** contains a very similar pattern in the upfield region of the  $^1\text{H}$  NMR to the parent oxime, indicating that little change in environment had occurred to the rest of the molecule.

### 2.2.5.5.3 Intramolecular nitrone formation

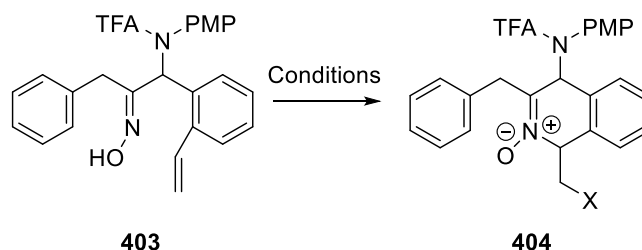
Due to the problems associated with the lack of *O*- and *N*-alkylation of **359**, it was thought that intramolecular alkylation of an oxime might be possible, via a Grigg-type reaction. Hence a tethered alkene-type  $\beta$ -nitroacetamide **102ad** (prepared in other work: see section 2.3.2) was prepared (**Scheme 146**). Reduction of the nitro group using  $\text{CrCl}_2$  as previously described led to formation of oxime **403** in only moderate yield (**Scheme 135**).



**Scheme 135.** Formation of tethered alkene oxime **403**

Characterisation of oxime **403** showed retention of the alkene with peaks at  $\delta$  5.30 ppm (1H, dd,  $J = 11.0, 1.2$ ,  $\text{ArCHCH}_2\text{-cis}$ ), 5.57 ppm (1H, dd,  $J = 17.2, 1.2$ ,  $\text{ArCHCH}_2\text{-trans}$ ) and 6.54 ppm (1H, dd,  $J = 17.2, 11.0$ ,  $\text{ArCHCH}_2$ ) (**Fig. 8**). Interestingly, whilst the  $-\text{OH}$  peak for oxime **359** was not present in the  $^1\text{H}$  NMR spectrum, oxime **403** contained a singlet peak at  $\delta$  7.43 ppm without COSY/HSQC couplings; HMBC data showed couplings to the signals at  $\delta$  33.2 ppm ( $\text{ArCH}_2$ ) and  $\delta$  156.2 ppm (q,  $\text{CNOH}$ ), hence this was assigned as the  $-\text{OH}$  peak. IR spectroscopy confirmed the presence of an O-H stretch at  $\nu = 3414\text{ cm}^{-1}$  (analogous to that observed for the OH stretch for **359**). As **403** contained an N-OH peak, analysis of NOE interactions showed a correlation between  $\delta$  7.43 ppm (1H, s, N-OH) and the benzylic  $\text{CH}_2$  signal at  $\delta$  4.30 (1H, d,  $J = 15.7$ ,  $\text{PhCH}_2$ ), no interactions were observed between the N-OH peak and signals for  $\text{CHN}$  or alkenyl peaks, hence oxime **403** was assigned as the (*E*)-isomer.

Oxime **403** was then subjected to various conditions to obtain the corresponding nitrone (**Table 14**). Primary reactions attempted for the formation of nitrone **404** (X = Br/I) included halogen-induced addition of the nitrogen to the alkene. Initial formation of a bromonium or iodonium species followed by nucleophilic 6-*exo*-attack should generate the nitrone with a residual halogen atom remaining on the *exo*-methyl group **404a**.



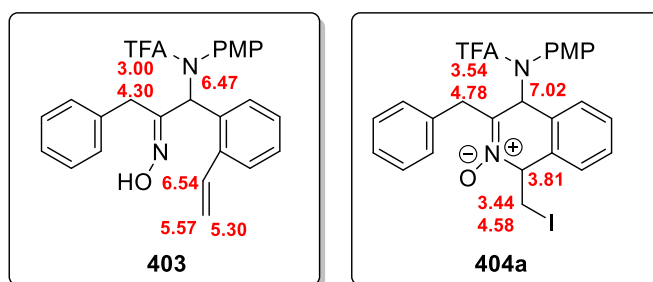
**Table 14.** Attempted intramolecular nitrone formation

Entry	Conditions	Solvent	Result
1	NBS, rt, 6 h	DCM	Complex mixture
2	I <sub>2</sub> , rt, 7 h	DCM	<b>404a</b> (X = I, 46 %)
3	Hoveyda-Grubbs II cat, CH <sub>2</sub> CHCO <sub>2</sub> Me	neat	SM

Initial reaction of oxime **403** with NBS (1.2 eq) resulted in degradation, giving a complex mixture after 6 hours. However addition of I<sub>2</sub> (1.2 eq) and stirring in the dark for 7 h resulted in the formation of a promising new product in < 46 % yield. The new product contained some impurity, which could not be removed, it was thought that this may be from decomposition during handling giving loss of iodine from the molecule. Examination by <sup>1</sup>H NMR of the new molecule (**Fig. 9**) showed the loss of alkenyl peaks from the parent oxime **403** at δ 5.30 ppm (1H, dd, *J* = 11.0, 1.2), 5.57 ppm (1H, dd, *J* = 17.2, 1.2) and 6.54 ppm (1H, dd, *J* = 17.2, 11.0) and an upfield shift of the benzylic CH<sub>2</sub> protons at δ 3.00 ppm (1H, d, *J* = 15.7) and 4.30 ppm (1H, d, *J* = 15.7) to δ 3.54 ppm (1H, dd, *J* = 14.2, 1.0) and 4.78 ppm (1H, d, *J* = 14.1) and CHN proton from δ 6.47 ppm (1H, br s) to 7.02 ppm (1H, d, *J* = 2.3) consistent with an increase in deshielding on formation of a nitrone. In addition, three new peaks were observed at δ 3.44 ppm (1H, *J* = 10.6, 3.0), 3.81 ppm (1H, m) and 4.58 ppm (1H, *J* = 10.6, 3.0), consistent with the alkyl group attached to the nitrone nitrogen atom. The proton signals at δ 3.44 & 4.58 correlated to a

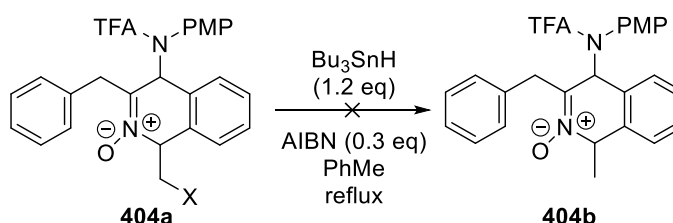


CH<sub>2</sub> peak at  $\delta$  11.1 ppm (HSQC) and coupled to the multiplet at  $\delta$  3.81 ppm (COSY). The upfield <sup>13</sup>C NMR shift at  $\delta$  11.1 ppm was hypothesized to be due to an  $\alpha$ -iodine atom. Disappearance of the oxime CNOH peak at  $\delta$  156.2 ppm (q) was observed, however the nitrone CNO peak could not be assigned. The product was therefore tentatively assigned as **404a**, no MS data was obtained.



**Fig. 9.** Assignment of nitrone **404a** *c.f.* oxime **403**

Due to the presence of the iodine atom in the molecule and its lability, its removal by radical de-iodination using TBTH (1.2 eq) and AIBN (0.3 eq) was attempted *in situ* (**Scheme 136**). Unfortunately degradation occurred leading to a complex mixture and no formation of desired product **404b**.



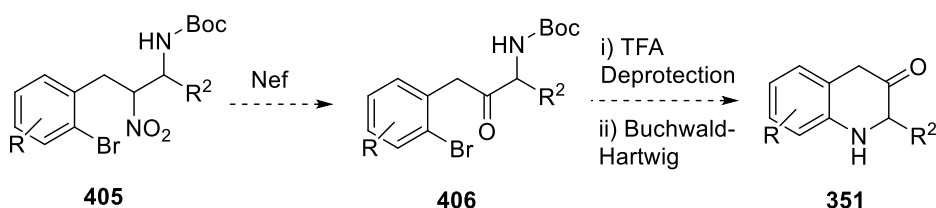
**Scheme 136.** Attempted radical de-iodination of nitrone **404a** *in situ*

Finally, attempted nitrone formation from oxime **403** via olefin metathesis of the tethered styrene was attempted. It is known that oximes undergo a concerted 1,3-azaprotio transfer reaction to electron-poor alkenes furnishing the *N*-alkylated derivative,<sup>213</sup> and it was thought that intramolecular addition of the oxime would occur spontaneously on formation of the electron-deficient styrene. Unfortunately olefin metathesis with methyl acrylate (as solvent) and Hoveyda-Grubbs II catalyst (10 mol %) at 80 °C in a vial (**Table 21**) proved unsuccessful (Entry 3, **Table 14**). No change was seen in the reaction, and starting material was recovered.

### 2.2.6 Conclusions and Future work

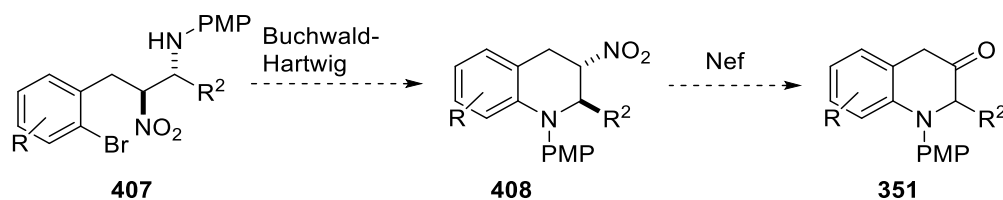
The Nef reaction of  $\beta$ -nitroacetamides **102aa** & **102ba** and  $\beta$ -nitroamine **357aa**, created via the nitro-Mannich reaction, have been attempted. The primary reaction attempted on  $\beta$ -nitroacetamide **102ba**, the reductive Nef using freshly prepared  $\text{CrCl}_2$ , has proved the only successful transformation, with the formation of an oxime intermediate **359**. Nef reactions performed via solvolytic, oxidative or other methods have proved unsuccessful due to an inbuilt propensity towards  $\beta$ -elimination on formation of a nitronate species; retro-addition of the  $\beta$ -nitroamine is also problematic. Further reactions of the oxime **359** were briefly studied, including oxime hydrolysis, Beckmann rearrangement and nitron formation. These reactions also proved temperamental, hence the Nef reaction was abandoned in favour of more successful radical research.

Future work in this area is limited due to the range of problems encountered, as previously described in this chapter. Possible avenues for investigation are described below. Investigation of the Nef reaction of *N*-Boc protected  $\beta$ -nitroamines may prove more successful due to successful reports of success in this area.<sup>16, 88d, 132b</sup> Previous efforts in this group have seen the successful *N*-PMP deprotection, *N*-Boc re-protection strategy employed for the formation of a literature compound for analysis.<sup>190</sup> A protection swap for each molecule would be costly and unproductive, however if a nitro-Mannich reaction were run with an *N*-Boc protected imine, the Nef reaction could be directly performed on the nitro-Mannich adduct **405**. Cyclisation as previously described in the group could also be performed by subsequent *N*-Boc deprotection and Buchwald-Hartwig cyclisation to afford tetrahydroquinoline-3-ones **351** (Scheme 137).<sup>65</sup>



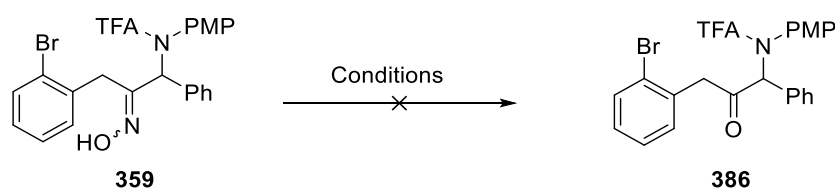
**Scheme 137.** Proposed Nef reaction of *N*-Boc  $\beta$ -nitroacetamides followed by cyclisation to tetrahydroquinoline-3-ones

Alternatively, direct cyclisation of  $\beta$ -nitroamines **407** followed by Nef reaction of the cyclised product **408** may be successful, due to the lack of a  $\beta$ -leaving group, leading to smooth Nef reaction (Scheme 138).



**Scheme 138.** Nef reaction of 3-nitrotetrahydroquinolines **408**

Further de-oximation reactions of oxime **359** could also be investigated, this work has only investigated a small range of the possible de-oximation reactions that are possible.



**Scheme 139.** De-oximation reactions

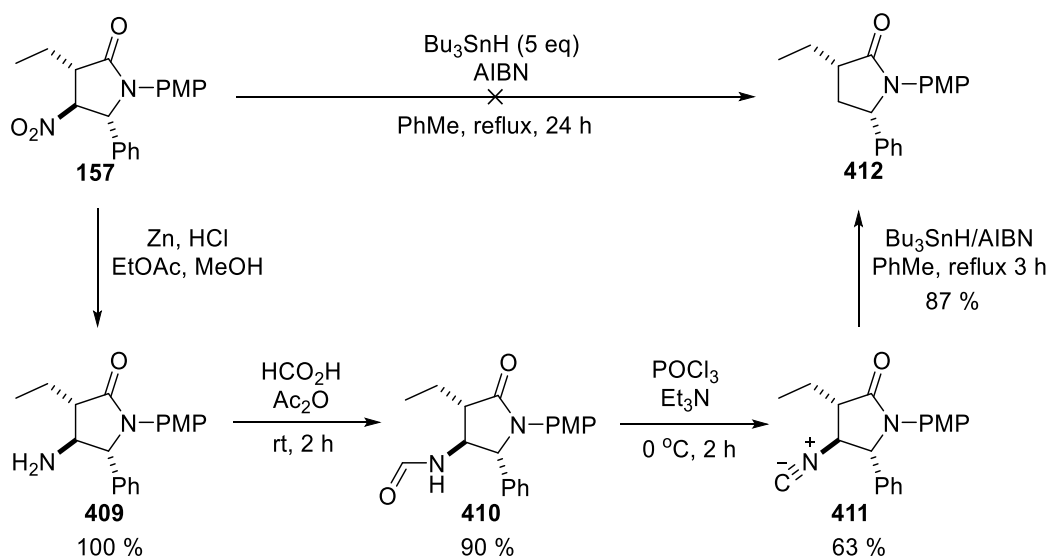
## 2.3 Radical Denitration of $\beta$ -nitroacetamides

### 2.3.1 Initial investigations

#### 2.3.1.1 Protodenitration of **102aa**

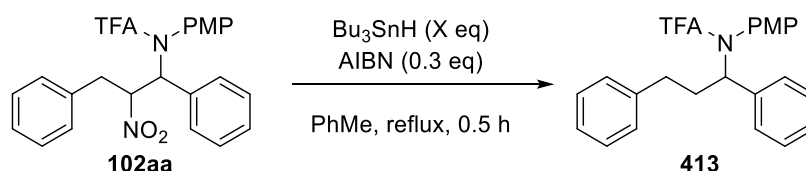
The reaction of  $\beta$ -nitroacetamides under radical generating conditions for the replacement of the nitro group with hydrogen or carbon-carbon bond formation required the formation of novel  $\beta$ -nitroacetamides via the nitro-Mannich reaction. In order to probe the feasibility of radical denitration of these compounds,  $\beta$ -nitroacetamide **102aa**, previously generated via the conjugate nitro-Mannich reaction conditions described by this group<sup>62</sup> (**Table 2**), was subjected to preliminary investigation. Most methods described for radical denitration, including the use of MeSNa,<sup>75c, 138</sup> KOH/ethylene glycol,<sup>139</sup> BNAH,<sup>140</sup> NaTeH<sup>141</sup> and TBTH,<sup>142-143</sup> are mainly limited to the denitration of tertiary nitro compounds<sup>75c, 138-139, 141</sup> or nitro compounds activated by an adjacent stabilising group (COR, CO<sub>2</sub>R, CN, Ar).<sup>140</sup> Ono showed that TBTH could be used for the denitration of unactivated secondary nitro compounds<sup>145</sup> under harsher conditions (toluene, reflux, 5 eq. TBTH). It should be noted that more recent methods that have become popular for the radical removal of various functional groups cannot be applied to the nitro group due to the undesired cleavage of the N-O bond.<sup>152, 154-155</sup> A search of the literature shows a focus on TBTH as the method of choice for radical denitration of secondary nitro compounds, with high variation in yield. Furthermore TBTH has previously been used in radical

denitration reactions of  $\beta$ -nitroamine derivatives (see section 1.4) and was thus picked as the reagent for radical denitration in this work. Previous work in this group focussed on the generation of  $\beta$ -nitroacetamides via the nitro-Mannich reaction, with only one example of attempted radical denitration of a secondary pyrrolidine-2-one derivative **157** using TBTH/AIBN (Scheme 140).<sup>58, 182</sup> In this case, radical denitration was achieved by use of an alternative reduction-deamination strategy via the formation of isocyanide **411**.



**Scheme 140.** Radical denitration performed by A. Kalogirou

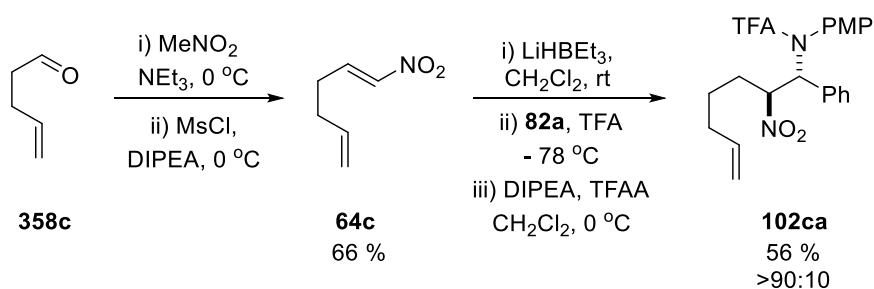
In contrast to the results obtained using pyrrolidine-2-one **157**, the results obtained from preliminary attempts at denitration of  $\beta$ -nitroacetamide **102aa** were more successful (Table 15). Initial reaction of **102aa** with TBTH (1.2 eq) and AIBN (0.3 eq) in toluene at reflux resulted in trace amounts of a possible denitration product. As expected, increasing the equivalents of TBTH resulted in higher yield, although disappointingly, the reported denitration conditions for secondary nitro compounds (5 eq, entry 3, Table 15) resulted in only 17 % yield. Pleasingly, a further increase in the equivalents of TBTH used (10 eq, 0.7 eq AIBN) resulted in the isolation of acetamide **413** in very good (79 %) yield (entry 4, Table 15). With these results in hand, application to the more interesting and useful addition of the intermediate radical formed to alkenes was investigated.

**Table 15.** Initial investigations into radical denitration of **102aa**

Entry	X	% Yield <sup>a</sup> <b>413</b>
<b>1</b>	1.2	< 1
<b>2</b>	2	4 (4) <sup>b</sup>
<b>3</b>	5	17
<b>4</b>	10	79 <sup>c</sup>

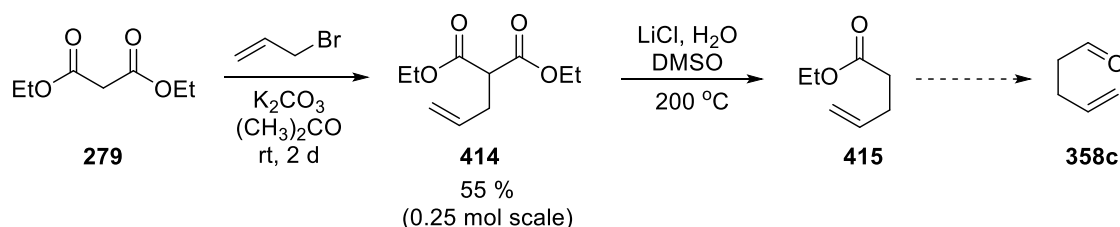
<sup>a</sup>isolated yield <sup>b</sup>reaction run in benzene <sup>c</sup>0.7 eq AIBN**2.3.1.2 Initial formation of a 5-hexen-1-yl tethered  $\beta$ -nitroacetamide**

The investigation of the addition reactions of radicals formed via denitration of  $\beta$ -nitroacetamides was initiated with the formation of the simplest precursor based on the 5-hexen-1-yl radical template. It was envisaged that this molecule would form the backbone of the  $\beta$ -nitroacetamide alkene tether, and could be derivatised before or after installation, leading to a range of novel radical cyclisation precursors. Formation of nitroalkene **64c** from aldehyde **358c** was achieved in good yield via the procedure described for aliphatic aldehydes in previous work (**Scheme 141**). Formation of  $\beta$ -nitroacetamide **102ca** was achieved upon conjugative nitro-Mannich reaction of nitroalkene **64c** with Superhydride ( $\text{LiHBEt}_3$ ) followed by trapping of the nitronate with imine **82a** and TFA protection (General procedure F).

**Scheme 141.** Formation of tethered alkene  $\beta$ -nitroacetamide **102ca**

The product  $\beta$ -nitroacetamide **102ca** was achieved in good (56 %) yield (**Scheme 141**), and was obtained as a mixture of diastereoisomers (> 90:10) by  $^1\text{H}$  NMR. In line with previous work conducted in this group,<sup>62, 65</sup> and as previously mentioned, the  $\beta$ -nitroacetamide **102ca** is assigned as the major *anti*- isomer. However, the loss of stereochemical integrity that takes place on formation of the radical negates any need for specificity in the nitro-Mannich reaction.

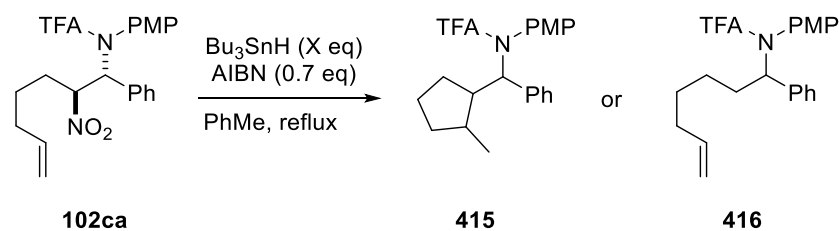
Aldehyde **358c** was itself originally prepared via Swern oxidation of pent-4-enol, however this reaction proved capricious; attempted formation of **358c** in bulk via allylation of diethyl malonate, followed by decarboxylation and reduction also proved problematic due to the volatility of intermediate **415**.



**Scheme 142.** Attempted bulk formation of aldehyde **358c**

### 2.3.1.3 Investigation of radical cyclisation and further modifications

With the first tethered alkene precursor **102ca** in hand, radical denitration-cyclisation was attempted. Our initial investigations of radical denitration of **102aa** had shown that 10 eq of TBTH was required for an efficient reaction (Entry 4, **Table 15**). However whilst 5-hexen-1-yl radical cyclisations are known to be extremely fast, at high concentrations of TBTH the rate of hydrogen abstraction increases and competing hydrogen abstraction from TBTH becomes increasingly problematic. It was decided to attempt the reaction with fewer equivalents of TBTH, and it was hoped this would lead to the cyclisation product **415** in preference to protodenitration product **416** (**Table 16**).

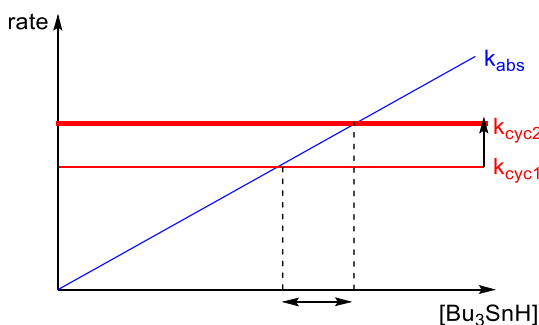
**Table 16.** Attempted radical denitration-cyclisation of **102ca**

Entry	X	Result	% Yield
1	5	Complex mixture	-
2	10	Protodenitration	<b>415<sup>a</sup></b> & <b>416</b> (60)

<sup>a</sup>Inseparable from protodenitration compound **416**, ~30 % by <sup>1</sup>H NMR

Unfortunately, radical denitration of **102ca** using fewer equivalents seemed to result in a complex mixture of starting material, possible cyclopentane diastereoisomers **415**, an unidentified compound (trace amount) which could be the *endo*-cyclised product, and decomposition products (Entry 1, **Table 16**). The presence of possible nitroalkene formed via elimination of TFA-NH-PMP **364** was observed in the crude <sup>1</sup>H NMR. Elimination under high temperatures is known to occur in compounds of this type.<sup>12</sup> It appeared that subjecting the β-nitroacetamide **102ca** to the high temperature (110 °C) of refluxing in toluene led to decomposition via elimination of the trifluoroacetamide **364** as previously seen in investigations in to the Nef reaction (see section 2.2.3). Analysis of the possible cyclopentane product from the complex mixture gave no expected molecular peak for cyclopentane **415** (391.2), however a peak was seen at 390 (M + H<sup>+</sup>), which could correspond to an oxidised cyclopentane molecule, however it is unclear how this would occur. The <sup>1</sup>H NMR spectrum showed the presence of doublets at δ 0.70 (*J* = 6.9) and δ 1.04 (*J* = 6.9) ppm suggesting a cyclopentyl methyl group. However the <sup>1</sup>H NMR was a complex mixture of products and it was difficult to glean much more information; the ratio of methyl peaks could not be determined due to overlap of the peak at δ 1.04 ppm with other peaks. The recovery of starting β-nitroacetamide **102ca** was not unexpected, as fewer equivalents of TBTH leads to a lower yield of protodenitration (**Table 15**). Returning to the optimised conditions for protodenitration (Entry 2, **Table 16**) resulted in the isolation of protodenitration product **416** in good yield, which co-eluted with a small amount (~30 %) of cyclisation product **415**, which could not be isolated. Unfortunately

these results presented a conundrum; too few equivalents of TBTH resulted in a complex mixture, with decomposition of the  $\beta$ -nitroacetamide under the longer reaction times and high temperatures, however use of 10 eq TBTH resulted in a fast protodenitration reaction. A solvent switch to the lower boiling benzene was envisaged as way to counteract the decomposition at high temperatures, however radical denitration of secondary compounds is known to be unfavourable and requires high temperatures for cleavage of the C-N bond.<sup>137a, 145</sup> It was hypothesised that radical denitration in benzene could be successful but may require long reaction times and higher equivalents of TBTH to effectively propagate the radical chain. The conditions required for removal of the nitro group presented the subsequent radical cyclisation step with a high concentration of TBTH, thus increasing the rate of hydrogen abstraction ( $k_{\text{abs}}$ ). A rise in the value of  $k_{\text{abs}}$  vs  $k_{\text{cyc1}}$  would lead to a higher proportion of the undesired product **416**, however if the rate of cyclisation was increased ( $k_{\text{cyc1}}$  to  $k_{\text{cyc2}}$ , **Fig. 10**), a wider window for cyclisation could be opened up in which a higher concentration of TBTH ( $[\text{Bu}_3\text{SnH}]$ , **Fig. 10**) could be used without compromising cyclisation of the radical. Thus an alkene tether more favourable to cyclisation was sought.



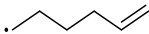
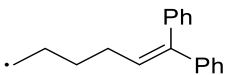
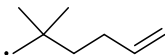
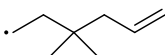

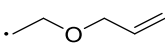
**Fig. 10.** Hydrogen abstraction vs cyclisation

Modification of the alkene tether could proceed via two main pathways leading to probable faster cyclisation. The simplest modification of the alkene tether that could be attempted would be the installation of electron-stabilising groups on to the end of the alkene. The orbital interaction of the nucleophilic radical SOMO with the electron poor alkene LUMO would be favourable as they are closely matched in energy, leading to an acceleration of  $k_{\text{cyc}}$ . Alternatively, restructuring of the alkene tether backbone was considered; this could be installed during the nitro-Mannich reaction itself, or as a post-modification. A wide variation of 5-hexen-1-yl type radical cyclisations are known, with available cyclisation rates (**Table 17**).<sup>214</sup> Substitution of the tether can increase the rate via the *gem*-dimethyl effect, this is seen by the substitution at C-2, C-3 or C-4 by two



methyl groups (Entry 1 vs entries 3 – 5, **Table 17**); the lone pairs of oxygen provide a heightened effect on replacement of C-3 (Entry 6). Although a combination of theories account for this increase in rate by increased substitution in ring cyclisation, the formation of medium-sized rings is thought to be accelerated by increased gauche interactions, holding the reactive centres in close proximity.<sup>215</sup> It was hypothesised that by increasing the population of proximate reactive centre rotamers of  $\beta$ -nitroacetamides, faster cyclisation could be achieved; this would enable more equivalents of TBTH to be used at a lower temperature, leading theoretically to higher yielding radical cyclisations.

**Table 17.** Measured rates of cyclisation of some 5-hexen-1-yl radicals<sup>214</sup>

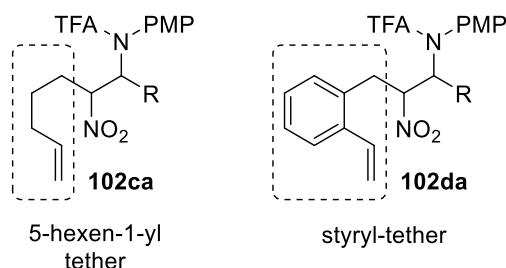
Entry <sup>a</sup>	Tether	$k_{\text{cyc}} / \text{s}^{-1}$
1		$2.4 \times 10^5$
2 <sup>b</sup>		$4 \times 10^7$
3		$3.6 \times 10^6$
4		$5.1 \times 10^6$
5		$3.2 \times 10^6$
6		$8.5 \times 10^6$

<sup>a</sup>At 25 °C <sup>b</sup>at 20 °C

### 2.3.2 Development of styryl tethered $\beta$ -nitroacetamides

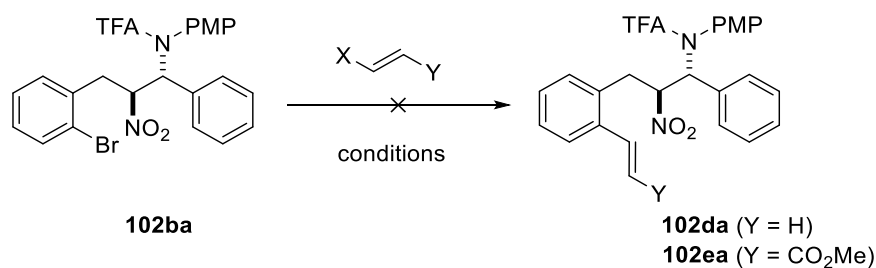
A variety of modifications to the 5-hexen-1-yl tether could be attempted, however compliance with the conditions of the nitro-Mannich reaction were necessary; any post-nitro-Mannich modifications must be feasible without degradation of the parent  $\beta$ -nitroacetamide. As part of work towards the Nef reaction, a 2-bromobenzyl  $\beta$ -nitroacetamide was synthesised (**Table 2**). It was hypothesised that this bromide could form the basis for a coupling reaction in order to install various styryl-type tethers **102da** for radical cyclisation (**Fig. 11**). In comparison to the parent 5-hexen-1-yl type tether **102ca**, a reduction in the possible conformations of the tether is introduced by the presence of a benzene ring which spans the two carbon atoms adjacent to the alkene. The

degrees of rotational freedom observed by the alkane chain is reduced by both the planarity of the  $sp^2$  framework of the benzene ring and also the steric bulk it provides. Although rotation of the alkene away from the reactive centre is possible, the number of tether conformations would be reduced, in a variation of the reactive rotamer effect.<sup>215</sup> The probability of the alkene being in proximity to the radical formed is higher than then parent 5-hexen-1-yl radical; it was thought this may result in a higher  $k_{cyc}$  value, and therefore a higher probability of success.



**Fig. 11.** Proposed styryl tether

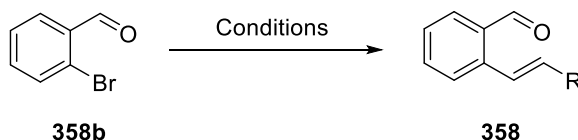
Initial investigations into the direct vinylation, alkylation or Heck reaction of bromide **102ba** were unsuccessful. Attempted coupling of **102ba** with vinyl magnesium chloride<sup>216</sup> using  $PdCl_2(dppf)$  led to a complex mixture, as did Heck reaction with methyl acrylate<sup>217</sup> using  $Pd(OAc)_2/PPh_3/NEt_3$ ; formation of an aryl Grignard from **102ba** for iron (III) coupling with vinyl bromide<sup>218</sup> was also attempted, but unsuccessful (**Scheme 143**).



**Scheme 143.** Attempted vinylation of **102ba**

The lack of success directly from  $\beta$ -nitroacetamide **102ba** led to the investigation of alkene tether incorporation prior to the nitro-Mannich reaction. Vinylation and Heck reactions of 2-bromobenzaldehyde were attempted (**Table 18**). Initial vinylation of 2-bromobenzaldehyde **358b** with potassium vinyltrifluoroborate **417** led to a complex mixture (Entry 1), however under homogeneous conditions<sup>219</sup> the reaction proceeded in good yield to product **358d** (Entry 2). Heck reaction of 2-bromobenzaldehyde with

methyl acrylate **418** afforded the desired product **358e** by coupling with Pd(OAc)<sub>2</sub> (Entry 3); use of PdCl<sub>2</sub> under phase transfer conditions resulted in a complex mixture (Entry 4).

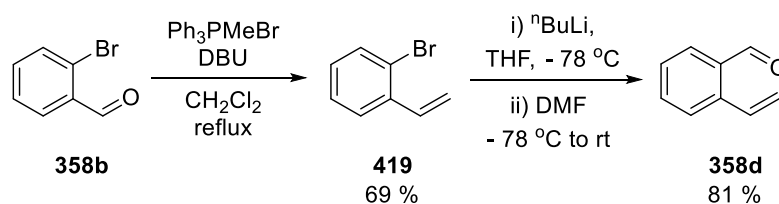


**Table 18.** Vinylation/Heck reaction of 2-bromobenzaldehyde

Entry	alkene	conditions	Result	% Yield <sup>a</sup>
<b>1</b>	<chem>C=CC(F)(F)F.[K+]</chem> <b>417</b>	PdCl <sub>2</sub> (dppf), NEt <sub>3</sub> , <sup>n</sup> PrOH	Complex mixture	-
<b>2<sup>219</sup></b>	<chem>C=CC(F)(F)F.[K+]</chem> <b>417</b>	PdCl <sub>2</sub> , Cs <sub>2</sub> CO <sub>3</sub> , THF-H <sub>2</sub> O	<chem>O=Cc1ccccc1C=C</chem> <b>358d</b>	57
<b>3<sup>217</sup></b>	<chem>C=CC(=O)OC</chem> <b>418</b>	Pd(OAc) <sub>2</sub> , PPh <sub>3</sub> , NEt <sub>3</sub>	<chem>COC(=O)C=Cc1ccccc1C=O</chem> <b>358e</b>	45
<b>4</b>	<chem>C=CC(=O)OC</chem> <b>418</b>	PdCl <sub>2</sub> , Bu <sub>4</sub> NBr, Na <sub>2</sub> CO <sub>3</sub>	Complex mixture	-

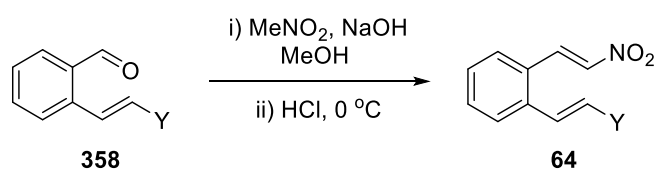
<sup>a</sup>isolated yield

Unfortunately it was discovered that whilst initially successful, the vinylation of 2-bromobenzaldehyde **358b** with potassium vinyltrifluoroborate **417** was capricious and did not work on a large scale. Hence an alternative route to 2-vinylbenzaldehyde **358d** was sought. Conversion of 2-bromobenzaldehyde **358b** to 2-bromostyrene **419** via a Wittig reaction using Ph<sub>3</sub>PMeBr/DBU followed by halogen-lithium exchange and trapping with DMF was found to be an efficient, scalable (24 g, 0.13 mol **358b**) route to 2-vinylbenzaldehyde **358d** (Scheme 144).<sup>220</sup>



**Scheme 144.** Scalable formation of **358d**

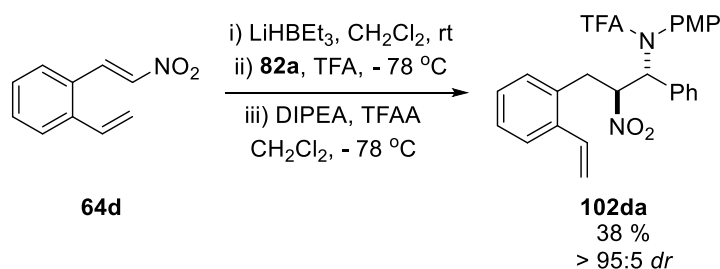
With 2-vinylbenzaldehyde **358d** and its methyl acrylate derivative **358e** in hand, we then sought to synthesise the corresponding nitro-Mannich precursors. Initial attempts focussed on the generation of nitroalkenes **64** via general procedure B (**Scheme 119**) previously reported in the group for the synthesis of aryl nitroalkenes.<sup>62, 65</sup> To our satisfaction, 2-vinylnitrostyrene **64d** was afforded in high yields under these conditions (Entry 1, **Table 19**). However the same conditions afforded a complex mixture from the methyl acrylate derivative **358e** (Entry 2). General procedure D, stirring **358e** overnight in MeNO<sub>2</sub>/NEt<sub>3</sub> also resulted in a complex mixture. It is likely that the 1,4-addition of nitromethane or other nucleophiles generated in the reaction into the methyl acrylate moiety and possible ester hydrolysis under basic or acidic conditions can lead to a complex array of products derived from this reaction.



**Table 19.** Formation of vinyl nitrostyrenes

Entry	Y	Result	% Yield
1	H ( <b>358d</b> )	<b>64d</b>	85
2	CO <sub>2</sub> Me ( <b>358e</b> )	Complex mixture	-

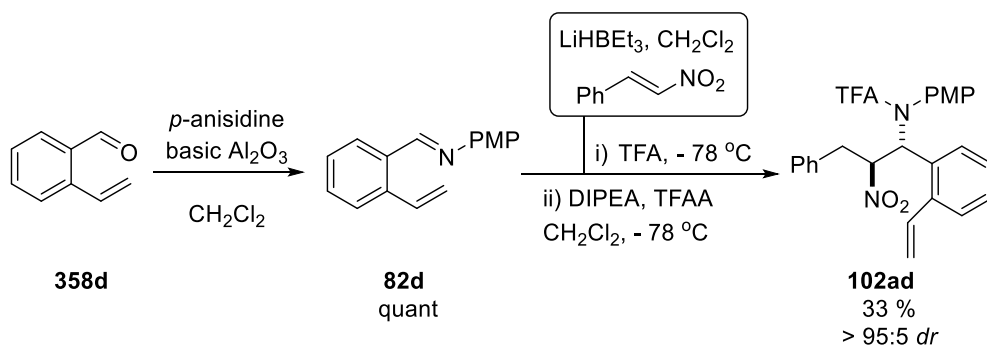
The reductive nitro-Mannich reaction of nitroalkene **64d** with simple benzyl *N*-PMP imine **82a** was then attempted. This reaction was successful, with a yield of 38 % over two steps (**Scheme 145**) and as essentially one diastereomer (> 95:5 *dr*). However, the low yield was problematic, leading to a bottleneck at the nitro-Mannich step. It was found that over a range of scales, the reaction afforded yields consistently between 33 – 38 %, with greater yields observed on larger scale (> 1 g).



**Scheme 145.** Reductive nitro-Mannich reaction of **358d**

The equivalent nitro-Mannich reactions of *trans*- $\beta$ -nitrostyrene **64a** and its 2-bromo derivative **64b** (Table 2) result in yields of 62 – 66 %, and in the case of the bromide, the bulky bromine atom on the styrene ring caused little erosion in yield. Analogous reactions of 2-methyl, 2-methoxy or 2-trifluoromethyl nitrostyrenes have been shown in previous work to give drops in yield of between 3 -10 %. The significant drop in yield for the vinyl-derivative **358d** may have been caused by side reactions of the styrene moiety; this may include polymerisation,<sup>221</sup> TFA-catalysed nucleophilic addition to the styrene<sup>221</sup> or other possible reactions of the styrene<sup>222</sup> and was less likely to be attributed to steric bulk alone.

A similar yield was obtained for the nitro-Mannich reaction of 2-vinylimine **82d**, prepared from 2-vinylbenzaldehyde **358d**, and *trans*- $\beta$ -nitrostyrene **64a**. Formation of the *N*-PMP imine was achieved as in general procedure A (Scheme 118); condensation with *p*-anisidine gave the crude imine **82d** in quantitative yield. Reaction of imine **82d** with the reduced *trans*- $\beta$ -nitrostyrene in the presence of TFA, followed by TFAA protection afforded  $\beta$ -nitroacetamide **102ad** in 33 % yield as essentially one diastereomer (Scheme 146). The low yield for the styryl-derivative **102ad** supports the hypothesis that the styrene, as the limiting reagent, undergoes degradation during the reaction, leading to moderate yields.

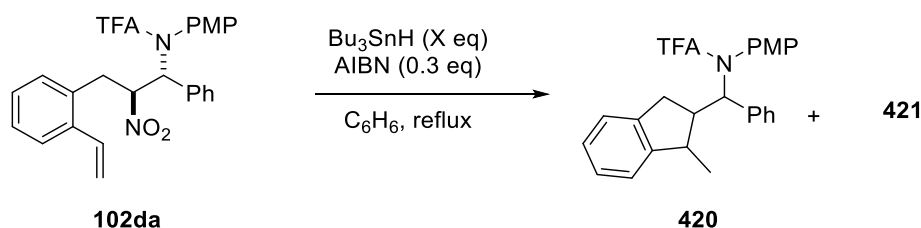


**Scheme 146.** Reductive nitro-Mannich reaction of **102ad**

### 2.3.3 Radical cyclisation of the styryl tethered radical precursors

#### 2.3.3.1 Investigation of the radical cyclisation of styryl tethered $\beta$ -nitroacetamide **102da**

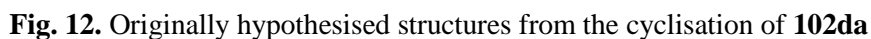
With styryl-tethered  $\beta$ -nitroacetamide **102da** in hand, we then focussed on development of the radical cyclisation of these secondary nitro groups. As previously discussed, it was hypothesised that a styryl tether may offer a more rapid rate of cyclisation due to the planarity of the benzene substituted 5-hexen-1-yl radical; it was hoped that this would allow a higher concentration of TBTH before  $k_{\text{abs}} > k_{\text{cyc}}$ . The reactions were run in benzene at reflux, thus at a lower temperature to avoid degradation of the  $\beta$ -nitroacetamides **102**. The concentration of **102da** was 0.034 M on a 50 mg (0.1 mmol) scale, TBTH concentration was dependent on the equivalents used. A range of equivalents (TBTH) from 2.5 – 10 was tested in order to find the best cyclisation conditions (**Table 20**).



**Table 20.** Intramolecular radical denitration-cyclisation of a secondary  $\beta$ -nitroacetamide optimisation

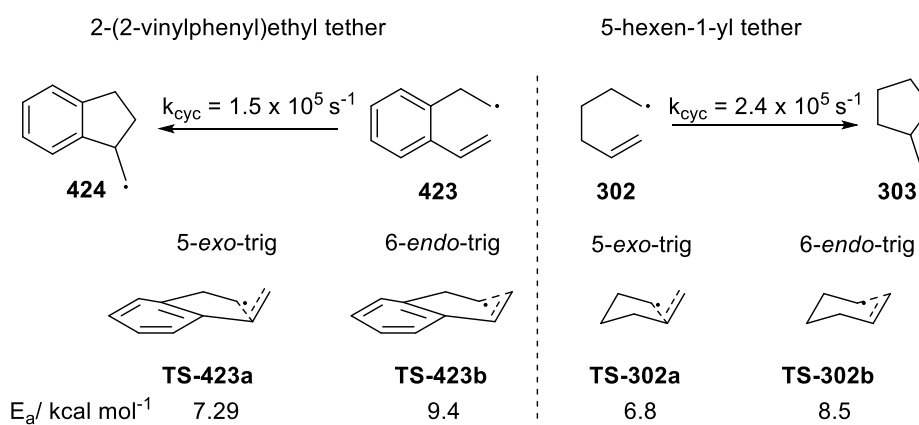
Entry	X	Result	<b>420:421<sup>a</sup></b> ( <b>420 dr</b> )	% Yield ( <b>SM:420:421</b> ) <sup>b</sup>
<b>1</b>	2.5	Mainly <b>102da</b> , trace of <b>420</b>	-	-
<b>2</b>	5	SM:Products (10:90)	75 <sup>c</sup> :25 (40:20 <sup>c</sup> :40:0)	11:18:23
<b>3</b>	10	SM:Products (~10:90)	>75 <sup>c</sup> :25 (40:20 <sup>c</sup> :40:0)	12:38:20
<b>4<sup>d</sup></b>	2.5	Complex mixture	-	-

<sup>a</sup>From crude <sup>1</sup>H NMR after partitioning with MeCN/Hexanes <sup>b</sup>Isolated yield <sup>c</sup>unknown exact value due to presence of tin residues <sup>d</sup>reaction run in PhMe



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cyclisations of 5-hexen-1-yl derived radicals.<sup>165</sup> The reason for this preference is attributed to the formation of an early, chair-like transition state of the radical tether **TS-302a**, which enables good overlap of the SOMO with the LUMO of the alkene; the long bond formed also provides an angle of attack of 106°, similar to that of unrestricted bimolecular attack (109°). On the other hand, the 6-*endo*-attack results in a highly strained transition state with poorer overlap of the SOMO and LUMO (**Scheme 147**).<sup>165</sup>



**Scheme 147.** Rates and energy barriers to cyclisation for two radical tethers

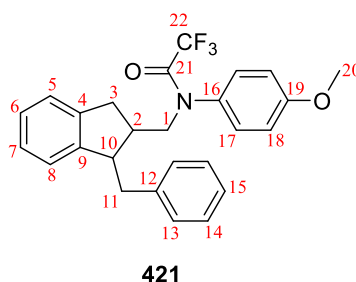
It was unclear whether the presence of the benzene ring in the chain would lead to a lowered energy barrier between the two cyclisations via a more planar transition state, giving rise to a higher proportion of the cyclohexyl-type product. In work performed using a similar styryl-type tether, no 6-*endo*-cyclisation was reported.<sup>169</sup> However reported calculations in the literature<sup>223</sup> suggest that for the parent 2-(2-vinylphenyl)ethyl radical **423**, a difference of ~2 kcal mol<sup>-1</sup> exists, favouring 5-*exo*- over 6-*endo*-cyclisation (**Scheme 147**). This is a similar energy barrier to that of the parent 5-hexen-1-yl radical **302**, for which an *exo:endo* ratio of 98:2 is observed,<sup>165</sup> hence the significant yield of the unidentified isomer **421** as the 6-*endo*-product **422** seemed unlikely. Interestingly, an increased barrier for cyclisation of the 2-(2-vinylphenyl)ethyl radical (7.29 kcal mol<sup>-1</sup>) compared with the 5-hexen-1-yl parent radical (6.87 kcal mol<sup>-1</sup>) was also reported; this suggests that substitution of the parent 5-hexen-1-yl radical **302** with a C=C bond leads to a more strained transition state, in which the geometrical approach of the radical to the alkene is less favourable.<sup>223</sup> This is also shown in the decreased rate of cyclisation reported for the 2-(2-vinylphenyl)ethyl radical **423** ( $k_{\text{cyc}} = 1.5 \times 10^5 \text{ s}^{-1}$ ) compared to the parent 5-hexen-1-yl tether **302** ( $k_{\text{cyc}} = 2.4 \times 10^5 \text{ s}^{-1}$ ).<sup>221</sup> With hindsight the rate of cyclisation would be expected to be slower for  $\beta$ -nitroacetamide **102da** vs  $\beta$ -



nitroacetamide **102ca**, however this was not observed in practice. At higher temperatures than the recorded  $k_{\text{cyc}}$  values at 25 °C, the required energy for distortion of the planarity in the 2-(2-vinylphenyl)ethyl tether may increase the favourability of the transition state **TS-423a**, and result in more rapid cyclisation of this tethered  $\beta$ -nitroacetamide, in line with observed yields.

### 2.3.3.2 1,4-radical aryl migration: analysis of isomeric product **421** and its formation

With this information in mind, it seemed unlikely that the unidentified isomer **421** was the 3-tetralyl isomer **422**, and more likely to be an indane derivative. Analysis by  $^1\text{H}$  and  $^{13}\text{C}$  NMR techniques also confirmed that this was an indane derivative (Full correlation table is given in the appendix). Initial analysis of the molecule was based around the assignment of the  $\text{CH}_2\text{N}$  peaks at  $\delta$  3.74 ppm (dd,  $J = 13.3, 5.3$ ) and  $\delta$  4.31 ppm (dd,  $J = 13.3, 9.8$ ), which corresponded to a  $\text{CH}_2$  unit at  $\delta$  52.0 ppm by HSQC analysis. Such deshielded peaks for a  $\text{CH}_2$  unit could be assigned to an electron-poor amine, in this case adjacent to the 2,2,2-trifluoroacetamide ( $\# = 1$ , **Fig. 13**); the shift at  $\delta$  52.0 ppm was low in comparison with the  $\text{CHN}$  peak for the initial denitration non-cyclised product **413** (**Table 15**) ( $\delta$  59.9 ppm), due to the loss of the adjacent aromatic ring. Retention of the PMP and TFA groups were confirmed by  $^{13}\text{C}$  NMR, with the usual quaternary carbons ( $\delta$  131.2 ppm,  $\text{ArCN}$ ) and ( $\delta$  159.9 ppm,  $\text{ArCO}$ ) and methyl peak ( $\delta$  55.6 ppm,  $\text{OCH}_3$ , also  $\delta$  3.84 ppm (3H, s,  $\text{OCH}_3$ ) by  $^1\text{H}$  NMR) and  $^{19}\text{F}$  NMR, with the expected peak at  $\delta$  -66.9 ppm (3F, s,  $\text{CF}_3$ ). It was clear that no aromatic ring had been lost, due to the presence of 9  $\text{ArH}$  by  $^1\text{H}$  NMR, hence it was hypothesised that a rearrangement had occurred, with a proposed structure **421**.

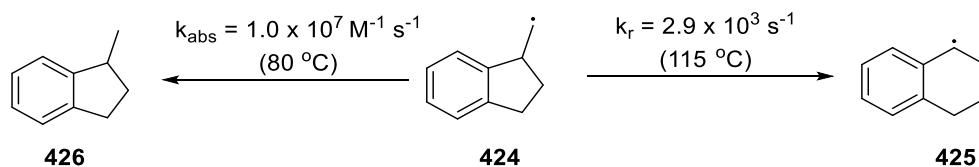


**Fig. 13.** Proposed structure of **421**

The proposed structure **421** was investigated by  $^1\text{H}$  and  $^{13}\text{C}$  NMR experiments, including HSQC and HMBC; a NOESY experiment was run to give an idea of the likely stereochemistry across the indane ring. It was known by DEPT and HSQC analysis that 3  $\text{CH}_2$  units were present in the molecule, at  $\delta$  35.2, 35.4 and 52.0 ppm by  $^{13}\text{C}$  NMR.

Ruling out the CH<sub>2</sub>N peak at  $\delta$  52.0 ppm, carbons 3 and 11 were assigned as either  $\delta$  35.2 or 35.4 ppm. The remaining aliphatic CH peaks at  $\delta$  41.5 and 48.0 ppm could be speculatively assigned as carbons 2 and 10 respectively due to their difference in shifts. Carbon 10 ( $\delta$  48.0 ppm) is adjacent to the aromatic ring of the indane and would likely be shifted further downfield than carbon 2. With a starting point of the CH<sub>2</sub>N (1, **Fig. 13**) peaks as previously mentioned, the coupling of these protons and the attached carbon to neighbouring protons/carbons was investigated (see correlation table, section 4.2.2). It was found that carbon 1 coupled to protons at positions 2 ( $\delta$  2.72 ppm, m) and 3 ( $\delta$  2.93 ppm, 2H, d,  $J$  = 8.2), confirming them in close proximity. Protons 2 and 3 were coupled to signals at  $\delta$  41.5 and 35.2 ppm in the HSQC spectrum; carbon 10 coupled by HSQC to a proton at  $\delta$  3.36 ppm (1H, dt,  $J$  = 10.2, 6.5). Carbon 10 also coupled to protons at 1, 1', 2, 3, and protons 11 and 11', which were assigned by this correlation, their benzylic shift (by <sup>1</sup>H and <sup>13</sup>C NMR of the corresponding carbon at  $\delta$  35.4 ppm), and HMBC couplings of C-11 to aromatic protons. Carbon 11 and its corresponding protons 11 and 11' by HSQC were further confirmed by couplings of C-11 to protons 2 and 10; a lack of coupling to protons 1,1' suggested that carbon 11 was the benzylic peak *exo* to the ring, and not in fact position 3. Carbon 3 is coupled to 1, 1' 5 and 10 which confirms its closer proximity to CH<sub>2</sub>N protons 1,1' and its presence in the indane ring. Further COSY analysis confirms the arrangement of the atoms with couplings between 1-2, 1'-2, 2-3, 2-10, 10-11, and 10-11' as the most diagnostic peaks. With structural assignment of the molecule consistent for the phenyl translocation product **421**, a check of the literature confirmed that radical attack on a benzene ring, followed by elimination to afford more stable acetamide-stabilised radicals was feasible. Many examples of radical aryl migrations are known.<sup>224</sup> A radical aryl migration not encountered within the investigation of the styryl-type tethered  $\beta$ -nitroacetamide **102da** is the neophyl rearrangement of methyl radical **424** following 5-*exo*-cyclisation (**Scheme 148**). The lack of observation of 3-tetralyl product **422** via rearrangement of the methyl radical is due to the relative rates of rearrangement ( $k_r$ ) and hydrogen abstraction ( $k_{abs}$ ). Beckwith<sup>225</sup> detailed that 5-*exo*-product **424** could undergo hydrogen abstraction to give **426** or undergo neophyl-type rearrangement to give the more thermodynamically stable 2-tetralyl radical **425** (**Scheme 148**). The rate constant for rearrangement ( $k_r = 2.9 \times 10^3 \text{ s}^{-1}$ ) is far slower than that of  $k_{abs}$  of a primary radical at 80 °C ( $k_{abs} = 1.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ ), giving  $k_r/k_{abs}$  of  $2.9 \times 10^{-4} \text{ M}$ . The rearrangement would only become relevant at low concentrations of TBTH. The concentration of TBTH in the radical cyclisation of  $\beta$ -

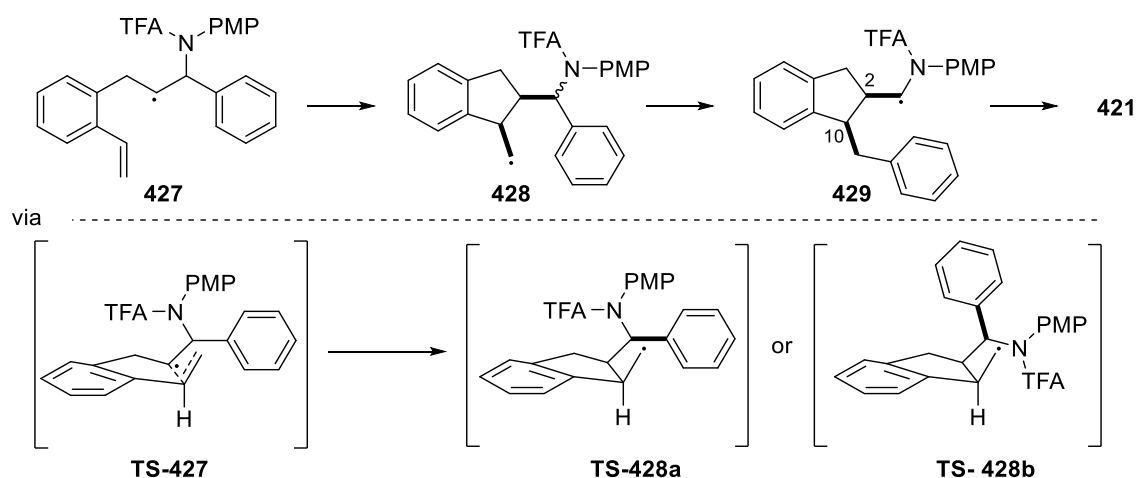
nitroacetamide **102da** was not low enough for the rearrangement to occur, with a range  $[\text{Bu}_3\text{SnH}]$  of 0.09 – 0.34 M using 2.5 - 10 eq TBTH. It is therefore unsurprising that no rearrangement of methyl radical **424** to 2-tetralyl radical **425** was observed.



**Scheme 148.** Neophyl rearrangement vs hydrogen abstraction of the methyl radical formed from cyclisation

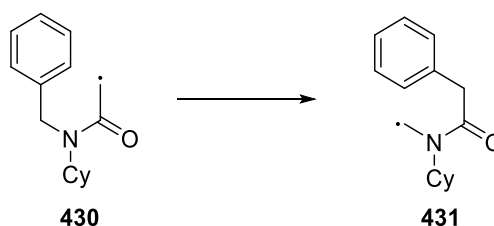
The rearrangement of unstable methyl radicals to more thermodynamically stable secondary or tertiary radicals is dependent on both the rate of rearrangement and abstraction of hydrogen, which is in turn dependent upon  $[\text{Bu}_3\text{SnH}]$ . In addition to the 1,4-aryl migration observed for  $\beta$ -nitroacetamide **102da**, three diastereoisomers of the unrearranged indane product **420** were also observed at  $[\text{Bu}_3\text{SnH}] = 0.17$  and  $0.34$  M (5 and 10 eq., entries 2 & 3, **Table 20**). In both cases, the ratio of **420**:**421** did not change, but remained at or very close to 75:25, suggesting that rearrangement was in this case less related to  $[\text{Bu}_3\text{SnH}]$ , but rather the product of a more favourable cyclisation that remained as favourable despite a twofold increase in  $[\text{Bu}_3\text{SnH}]$ . As only three isomers (at roughly 40:20:40:0 ratio by crude  $^1\text{H}$  NMR analysis of the reaction mixture) were observed, it was hypothesised that the fourth isomer may undergo 1,4-aryl migration due to favourable interaction of the methyl radical with the benzene ring (**Scheme 149**). In this case it would be assumed that all four isomers (A:B:C:D) may have been formed and that  $k_{\text{abs}} > k_{\text{r}}$  for three isomers (A,B,C); for the diastereoisomer (D) leading to **421**,  $k_{\text{r}} > k_{\text{abs}}$ . Alternatively it may be that one (or two) of the observed isomers (A,B or C) may undergo partial rearrangement and partial hydrogen abstraction, leading to the generation of both indanes **420** and rearrangement product **421**. With reference to the NOESY spectrum of **421** it was tentatively determined that the indane contained a *cis*-fused ring junction, due to the strong interaction between protons on carbons 2 and 10 (**Scheme 149**). Orientation of the methyl radical in a *cis*-fused ring towards the benzene ring appeared to be important for 1,4-aryl migration, as only one diastereoisomer of **421** was isolated. However, as the remaining three diastereoisomers could not be separated, the original orientation of the  $\text{CHN}(\text{TFA})(\text{PMP})$  moiety with respect to the *cis*-fused ring was unknown. The methyl radical **428** formed, *cis*:*cis* or *cis*:*trans*, was likely to be held in a more favourable

transition state for rearrangement to occur (**TS-428a** or **TS-428b**). Presumably either the *cis:cis* or *cis:trans* transition states is energetically more favourable, leading to more efficient overlap of the radical SOMO with the  $\pi$ -system of the benzene ring.



**Scheme 149.** Possible transition states for addition of the methyl radical to the benzene ring

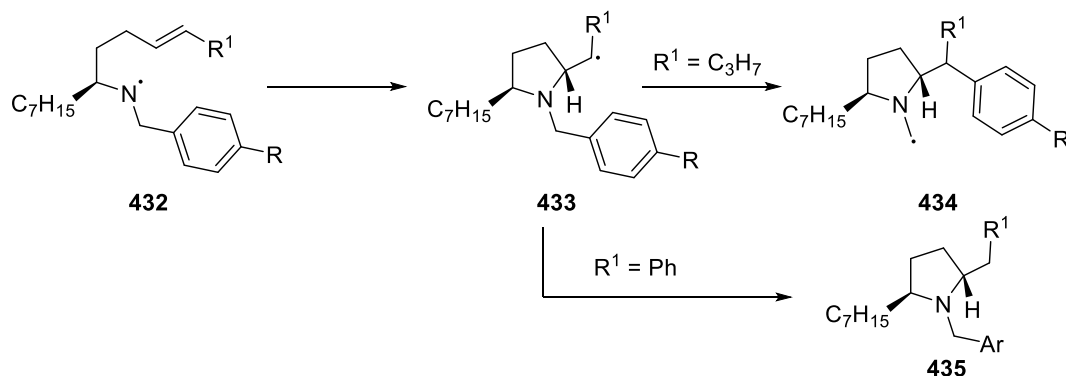
A range of 1,4-aryl migrations are described in the literature with a similar carbon-carbon bond cleavage step occurring adjacent to an amine or acetamide, resulting in the formation of stabilised carbon radicals. One such reaction proceeds via the formation of methyl  $\alpha$ -carbonyl radical **430**, which undergoes *ipso*-addition to the benzene ring, followed by cleavage of the carbon-carbon bond to afford primary radical **431** (**Scheme 150**).<sup>226</sup>



**Scheme 150.** Radical translocation of an aryl ring to give a more stable  $\alpha$ -amido radical

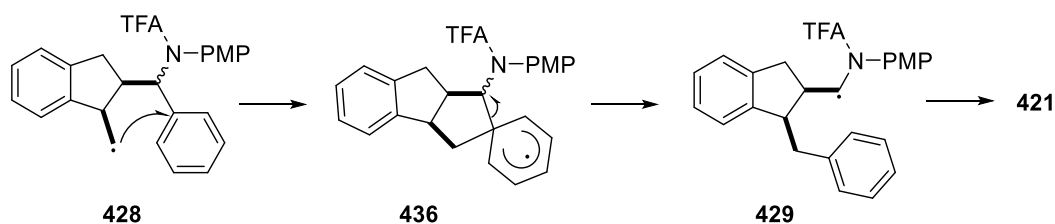
Similar yields of the hydrogen-abstraction product (40 %) and rearrangement product (31 %) were achieved, suggesting that although  $k_{\text{abs}} > k_r$ , the rate ( $k_r$ ) of *ipso*-substitution is very competitive with hydrogen abstraction at this dilution ( $\sim 10^{-4}$  M). A similar 1,4-migration following 5-*exo*-cyclisation of a nitrogen radical **432** was also described by Senboku and Tokuda;<sup>227</sup> migration of the benzene ring of radical **433** (when  $R^1 = C_3H_7$ ) is interesting as a primary  $sp^3$  radical **434** is formed at the expense of secondary  $sp^3$  radical **433** (**Scheme 151**). This shows the stabilising effect of the amine on the adjacent carbon

radical. The mechanism of substitution of the aryl ring was also thought in this case to proceed via 5-*exo*-trig addition of the radical at the *ipso*-position to generate an intermediate cyclohexadienyl radical, before cleavage of the carbon-carbon bond to give the  $\alpha$ -aminomethyl radical **434**. This was supported by the retention of substitution patterns on the migrating ring at both *meta*- and *para*- positions (**Scheme 151**).



**Scheme 151.** Radical 1,4-aryl migrations to give stable acetamide radicals

It was thought that a similar mechanism of substitution may exist for the 1,4-phenyl migration observed in the formation of indane **421** (**Scheme 152**). Attack of methyl radical **428** at the *ipso*-position of the aromatic ring would lead to spiro-cyclohexadienyl radical **436**, followed by preferable cleavage of the carbon-carbon bond leading to the more stabilised  $\alpha$ -amidoradical **429**, which then undergoes hydrogen abstraction to give the product **421**. The driving forces of the rearrangement were attributed to re-aromatisation and the stability of the  $\alpha$ -amidoradical.<sup>228</sup> Although similar reactions are performed at high dilution ( $\sim 10^{-4}$  M) leading to this rearrangement, it would appear that it occurs even at much higher concentrations (0.34 M) with reasonable yields (20 %, **421**). The mechanism could be confirmed by the formation of a  $\beta$ -nitroacetamide containing a substituted phenyl ring; retention of the substitution pattern would then confirm *ipso*-substitution. However, as this was not a desired fragmentation, a mechanistic investigation was not performed; of greater interest would be the cessation of the fragmentation reaction in order to obtain a higher yield of the indane **420**.

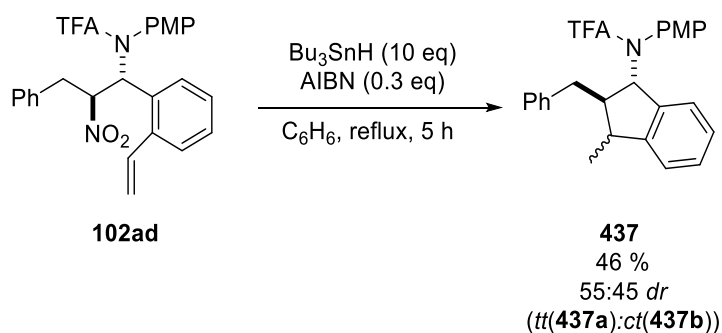


**Scheme 152.** Proposed mechanism for fragmentation of the indane methyl radical **428**

Tokuda reported that substitution of the alkene radical trap with a radical-stabilising group (Ph) led to no 1,4-aryl migration (**Scheme 151**), presumably due to the higher stabilisation of the secondary radical afforded by the aromatic ring.<sup>229</sup> It was thought that substitution of the styryl tether of  $\beta$ -nitroacetamide **102da** with stabilising groups ( $\text{CO}_2\text{R}$ ,  $\text{C(O)R}$ , CN, Ph) would lead to reduction of the competing rearrangement reaction due to the decrease in stabilisation afforded by rearrangement of a stabilised secondary radical to an  $\alpha$ -amidoradical, compared to that experienced by the methyl radical **428**. This 1,4-aryl rearrangement is undesirable as it does not lead to a value-added molecule due to the loss of a chiral centre; derivatisation of **102da** could lead to a similar benzyl-substituted indane ring.

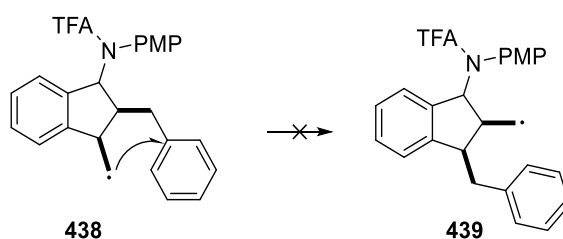
### 2.3.3.3 Radical cyclisation of complementary 2-(2-vinylphenyl) tether **102ad**

Derivatisation of the parent  $\beta$ -nitroacetamide radical precursor **102da** could be achieved via several routes in order to facilitate more efficient radical cyclisation. Complementary  $\beta$ -nitroacetamide **102ad**, with the styryl-tether on the imine portion of the molecule, had previously been successfully synthesised (**Scheme 146**), hence cyclisation of this molecule was attempted. Cyclisation of  $\beta$ -nitroacetamide **102ad** was run under the optimised conditions reported for **102da** (Entry 3, **Table 20**), resulting in cyclisation to 2-amidoindane **437** in good yield and a 55:45 *dr* (**Scheme 153**).



**Scheme 153.** Radical denitration-cyclisation of **102ad**

A further 11 % of indane was also isolated, however the  $^1\text{H}$  NMR indicated some decomposition may have occurred during purification as peaks were present in the indane mixture which were not present in the crude  $^1\text{H}$  NMR of the reaction mixture; it is unclear how this decomposition may arise. Interestingly, no evidence of fragmentation of the methyl radical occurred to give translocation of the phenyl ring as occurred with  $\beta$ -nitroacetamide **102da** was detected (**Scheme 152**). It was suggested earlier that one of the driving forces for this fragmentation is the formation of the more stable  $\alpha$ -amidomethyl radical **429**.<sup>228</sup> In the case of styryl tethered  $\beta$ -nitroacetamide **102ad**, the lack of an amido-stabilising group on the benzyl carbon renders the fragmentation much less favourable; a primary radical **439** would be formed from the translocation of the phenyl ring, hence it is not observed (**Scheme 154**).



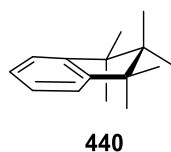
**Scheme 154.** Unfavourable fragmentation to form an unstabilised methyl radical

Characterisation of the indane **437** was very similar to that of its predecessor due to the structural similarity; a correlation table and table of important  $J$  couplings can be found in the appendix (see section 4.2.2). In this case, characterisation of the isomers was hindered by the inability to separate the diastereoisomers **437a** and **437b**, however attempts at characterisation proved successful by careful analysis by  $^1\text{H}$  and  $^{13}\text{C}$  NMR; a molecular peak at 439.2 ( $\text{M}^+$ ) confirmed the correct mass. The two main diastereoisomers had methyl peaks on the indane ring at  $\delta$  0.97 ppm (3H, d,  $J = 7.0$ ) and  $\delta$  1.12 ppm (3H, d,  $J = 7.3$ ); it was possible by a mixture of COSY, HSQC and HMBC techniques to identify which peaks aligned to which isomer. In most cases, the  $^1\text{H}$  NMR signals were easily identified, however three signals overlapping (of both diastereoisomers) at  $\delta$  2.96 – 3.04 ppm (3H, m) created a problem when assigning some COSY/HMBC correlations, however these were assigned as far as possible. The base signals for correlation of signals were the methyl peaks (above)  $\text{CHN}$  peaks at  $\delta$  6.28 ppm (1H, d,  $J = 8.8$ ) and  $\delta$  6.24 ppm (1H, d,  $J = 9.2$ ) and their corresponding carbon signals at  $\delta$  18.8, 17.3, 67.0 and 66.3 ppm. An attempt at assignment of the relative stereochemistry of the two diastereoisomers was made.

## 2.3.4 Stereochemical assignment of the products of radical cyclisation

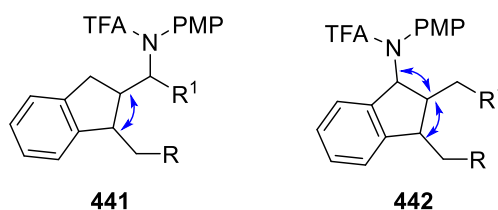
### 2.3.4.1 General considerations

Analysis of the stereochemistry of substituted cyclopentane rings by  $^3J_{\text{HH}}$  values is non-trivial. The Karplus equation links dihedral torsion angle  $\phi(\text{HCCH})$  with the corresponding  $^3J_{\text{HH}}$  values, forming a ‘Karplus relationship,’ which can aid the assignment of the dihedral angle  $\phi(\text{HCCH})$  and therefore the assignment of relative stereochemistry in a molecule by careful investigation of the  $^3J_{\text{HH}}$  values observed.<sup>230</sup> It is known that due to the different possible conformations of the cyclopentane ring (envelope or twist),  $J_{\text{trans}} > J_{\text{cis}}$  or  $J_{\text{cis}} > J_{\text{trans}}$  (Hz) depending on  $\phi(\text{HCCH})$  in a given conformer.<sup>231</sup> This leads to ambiguity in assigning  $^3J_{\text{HH}}$  values to a particular configuration, and hence difficulty in the assignment of relative stereochemistry. The assignment of indanes usually presents less of a challenge as the planarity of the aromatic ring leads to the adoption of an envelope-type structure **440** (Fig. 14) with variation in the puckering of the indane ring as a function of the size and electronegativity of the substituents.<sup>232</sup>



**Fig. 14.** Indane ring structure

It would be expected to a certain extent that indanes **440** containing the same or similar pattern of substitution, with little change in electronegativity of the substituents and bond length/angles, that some correspondence may be drawn between the relative orientations of substituents of given  $^3J_{\text{HH}}$  coupling values.<sup>232-233</sup> The structural similarity of the indanes of type **441** and **442** obtained via radical cyclisation led to the hypothesis that indanes with a similar stereochemical arrangement of substituents should display similar  $^3J_{\text{HH}}$  values, on reasonable deviation of the substituents at positions R and R<sup>1</sup> (Fig. 15).



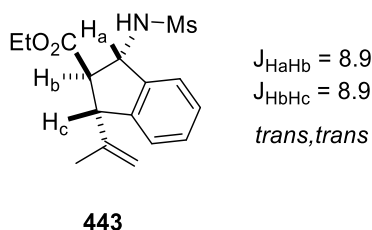
**Fig. 15.** Probable deviation of substitution possible with reasonable probability of similar  $^3J_{\text{HH}}$  values across the positions shown



Whilst the analysis of  $^3J_{\text{HH}}$  values should not be the sole basis of definitive assignment of a particular stereochemical arrangement, tentative correlations may be made in addition to the use of NOE data, and similarity in chemical shifts of the relevant protons. Any correlation of  $^3J_{\text{HH}}$  values with a concrete assignment of relative stereochemistry obtained from crystal structures (*vide infra*) would strengthen any assignments made. Tables of obtainable  $^3J_{\text{HH}}$  and NOE data for the relevant molecules can be found in the appendix.

#### 2.3.4.2 Stereochemical assignment of indane 437

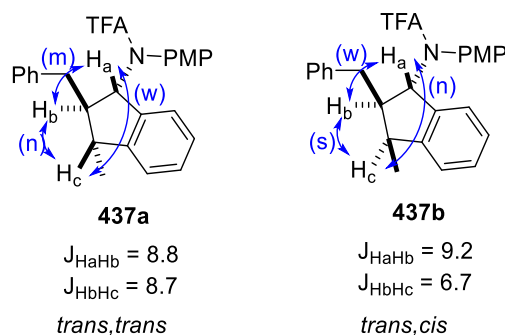
After the assignment of the  $^1\text{H}$  NMR, an analysis of the coupling constants and NOESY interactions was undertaken. Similar 2-amino-3-carbon substituted indane **442** derivatives in the literature display an approximate range of  $^3J_{\text{HH}}$  values  $\sim 8 - 9$  Hz (*trans* coupling) or  $6 - 8$  Hz (*cis* coupling).<sup>234</sup> Coupling constants for  $J_{\text{HaHb}}$  and  $J_{\text{HbHc}}$  were determined from  $^1\text{H}$  NMR analysis, with isomer **437a** displaying almost identical  $^3J_{\text{HH}}$  values  $J_{\text{HaHb}} = 8.8$  Hz and  $J_{\text{HbHc}} = 8.7$  Hz suggesting a similar relationship of proton orientation  $\phi(\text{HCCH})$  across both bonds: *trans,trans* or *cis,cis*. A very similar *trans,trans*-molecule in the literature, **443** displays similar  $^3J_{\text{HH}}$  values ( $J_{\text{HaHb}} = 8.9$  Hz and  $J_{\text{HbHc}} = 8.9$  Hz)<sup>234c</sup> (**Fig. 16**), further suggesting a possible *trans,trans*-orientation of indane **437a**.



**Fig. 16.**  $^3J_{\text{HH}}$  couplings of a similar 2-aminoindane

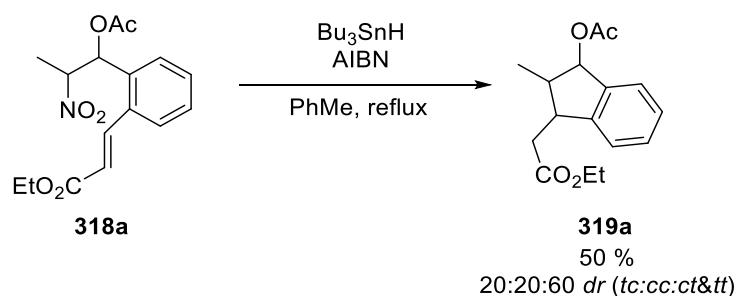
Analysis of the NOESY spectrum showed proton-proton interactions of  $\text{H}_a\text{-H}_b$  (m, medium) and  $\text{H}_b\text{-H}_c$  (n, no interaction). Interestingly, an interaction between  $\text{H}_a\text{-H}_c$  (w, weak) was also seen, suggesting that  $\text{H}_a$  and  $\text{H}_c$  were on the same face of the ring, therefore experiencing weak interaction. If a *cis*-H-H interaction occurs, strong (s) interaction between the protons in the NOESY spectrum would be expected, however as medium and no interaction was seen between  $\text{H}_a\text{-H}_b$  and  $\text{H}_b\text{-H}_c$  respectively, it could be inferred that the orientation of these protons with respect to each other is *trans*. With the similar  $J_{\text{HH}} \sim 8.8$  to literature compound **443** ( $J_{\text{HH}} 8.9$  Hz) and the information gleaned from NOESY interactions, the major isomer could be tentatively assigned as the *trans,trans*-isomer **437a**. Unfortunately, as the isomers could not be separated, obtaining a crystal structure for confirmation was not possible, however it was hoped any future

crystal structures that may be obtained would help to confirm this assignment (*vide infra*). Assignment of the minor diastereoisomer **437b** was undertaken in the same way. A similar  $J_{\text{HaHb}} = 9.2$  Hz suggested that  $\text{H}_a\text{-H}_b$  may have the same relative configuration as the major isomer ( $J = 8.8$  Hz) due to the  $J$  coupling similarity. However, the big difference in  $J$  coupling of  $\text{H}_b\text{-H}_c$  ( $J_{\text{HbHc}} = 6.7$  Hz, vs 8.7 Hz for **437a**) suggested a different relative orientation of the protons; this was confirmed by analysis of the NOESY spectrum, with  $\text{H}_b\text{-H}_c$  (s) meaning a likely *cis*-relationship. This was also supported by  $\text{H}_a\text{-H}_b$  (m) suggesting a possible *trans*- orientation and  $\text{H}_a\text{-H}_c$  (n), suggesting that these protons are not on the same face of the ring, and that diastereoisomer **437b** contains *trans,cis*-orientated substituents (**Fig 17**). In addition, the similarity in chemical shifts of the CHN proton ( $\delta$  6.28 ppm **437a** &  $\delta$  6.24 ppm **437b**) suggested similar relative stereochemistry  $\text{H}_a\text{-H}_b$  in both the major and minor isomers.



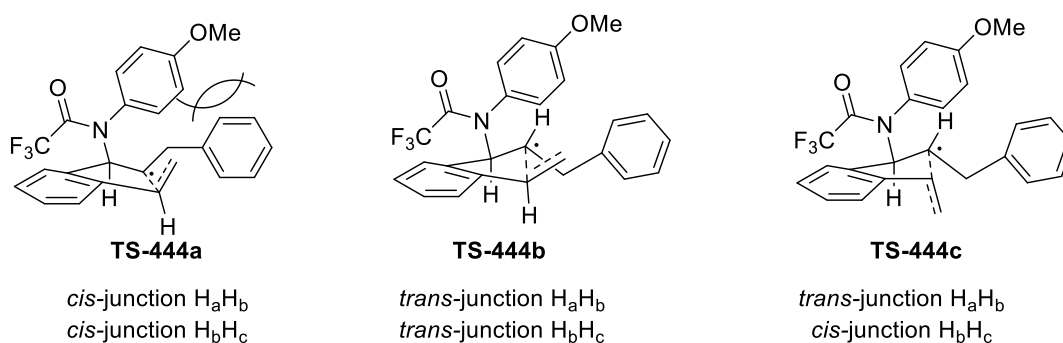
**Fig. 17.** Assignment of stereochemistry of 2-amidoindanes **437**; arrows show through-space (nOe) interactions

Interestingly, only the *trans,trans*- and *trans,cis*-orientated 2-aminoindanes were observed. This was in contrast to the 3 diastereomeric indanes **420** observed from cyclisation of radical **427** and *in situ* fragmentation of one of these 3 or a possible 4<sup>th</sup> diastereoisomer (**Scheme 149**). This suggested that the two possible transition states leading to the *trans,trans*- and *trans,cis*-diastereoisomers were more favourable than those of the *cis,cis*- or *cis,trans*-isomers, and that the energy difference between the *trans,trans*- and *trans,cis*- transition states was low, leading to a slight excess of *trans,trans*-**437a**. The most similar work investigating radical denitration of tertiary/secondary nitro groups and cyclisation of a similar styryl-type tether was reported by Luzzio.<sup>169</sup>



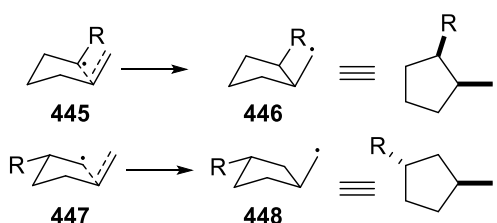
**Scheme 155.** Similar work by Luzzio giving a lower *dr*

Cyclisation of  $\beta$ -acetoxy nitro compound **318a** to 2-acetoxyindane **319a** was reported in a similar yield to that of  $\beta$ -nitroacetamide **437**, however diastereoselectivity was far lower. Luzzio reported a *dr* of 20:20:60 (*tc:cc:ct & tt*), compared to that reported here 45:0:55\* (\*no *ct*) (**Scheme 153**). It is likely that the much bulkier TFA-NH-PMP moiety contributes to the higher population of the two more energetically favourable transition states that lead to **437a** and **437b**. In the case of the  $\beta$ -acetoxy nitro compound **318a**, a very small difference in energy of the transition states may be observed due to the low steric bulk of acetate in comparison with the *N*-PMP-*N*-trifluoroacetamide. Luzzio assigned the relevant diastereoisomers via forming an ester linkage through acetate hydrolysis and lactonisation of the *cis*-isomer of a similar molecule, allowing separation, characterisation and extrapolation of the data to **319a**.<sup>169</sup> In order to justify the stereochemistry observed in the radical denitration-cyclisation reaction of **102ad** compared to its isomer **102da**, possible transition states were hypothesised (**Scheme 156**). Radical reactions tend to have early, reactant-like transition states, which do not necessarily reflect the thermodynamic stability of the products. Although 5-hexen-1-yl cyclisations are rapid, it is known that substitution at different positions of the tether in many cases affords predictable stereoselectivity to the product cyclopentane ring in line with a favourable arrangement of the substituents in a *pseudo*-chair or boat-like transition state.<sup>164b, 235</sup>



**Scheme 156.** Possible diastereomeric transition states for cyclisation of radical **444**

It was thought that similar *pseudo*-chair- or boat-like transition states may account for the high level of selectivity observed for  $\beta$ -nitroacetamide **102ad** in comparison with the unsubstituted  $\beta$ -nitroacetamide **102da**. The bulky *N*-PMP acetamide is placed equatorial, in order to minimise interactions with other substituents in the *pseudo*-chair-like 5-hexen-1-yl tether **TS-444**. In the case of the unobserved *cis*-H<sub>a</sub>H<sub>b</sub> relative stereochemistry **TS-444a**, this would require the *pseudo*-axial orientation of the benzyl group, leading to unfavourable steric interactions with the trifluoroacetamide or PMP protecting groups. However *trans*-H<sub>a</sub>H<sub>b</sub> orientation results in both the bulky *N*-PMP acetamide and benzyl groups in *pseudo*-equatorial positions around the ring (**TS-444b** & **TS-444c**). This minimises steric interactions, and it was thought this would lead to a lower-energy transition state.<sup>164b</sup> In contrast, **TS-444b** is only slightly favoured over **TS-444c**, as seen in the *dr* (55:45). Examination of the possible orientations of the methyl group showed that whilst *pseudo*-equatorial positioning of the methyl group would lead to the least steric hindrance with all groups held equatorially, repulsion between the methyl group in a *pseudo*-axial position with the neighbouring benzyl group was likely to be low, as the benzyl group is not sterically bulky. Interestingly, a major preference for the formation of the *cis*-isomer **446** of 5-substituted 5-hexen-1-yl radicals **445** is usually observed, which is thought to be due to a combination of steric and stereoelectronic effects.<sup>164b, 236</sup> This, coupled with usual cyclisation of 4-substituted 5-hexen-1-yl radicals **447** to the *trans*-stereoisomer **448** (**Scheme 157**)<sup>235</sup> suggest that the *trans,cis*-product may have been the expected product. It is likely in this case that a mixture of factors contribute to the energetic favourability of transition states **TS-444b** and **TS-444c**, including both steric and stereoelectronic effects. As previously mentioned, the benzene ring present in the radical tether presumably flattens<sup>223</sup> the *pseudo*-chair- or boat-like transition state, which may lead to differences in observed stereoselectivity compared to the unrestricted 5-hexen-1-yl tether **302**.

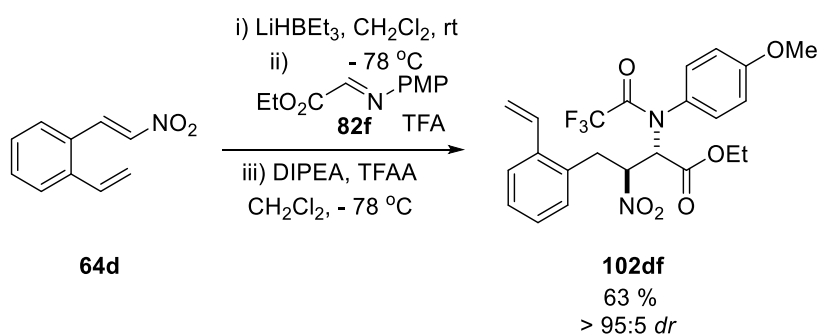


**Scheme 157.** Stereochemistry as a function of substitution pattern

### 2.3.5 Derivatisation of the styryl tether radical precursors

#### 2.3.5.1 Derivatisation of **102da** via imine variation

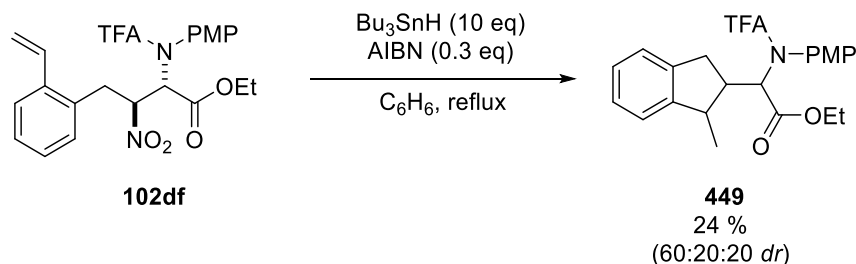
The first derivatisation of the initial  $\beta$ -nitroacetamide **102da** that was carried out was the use of a non-aromatic imine **82f**. The formation of a glyoxylate imine was thought to present a significantly different radical precursor. Although the addition of radicals to the C=O bond is disfavoured, in cases where addition is followed by a subsequent favourable and irreversible transformation, addition to the carbonyl can be a preparative reaction. Derivative **102df** would probe whether a similar fragmentation of the methyl radical would occur, in this case due to the driving force of a more stable  $\alpha$ -amidomethyl radical.<sup>228</sup> Formation of the glyoxylate imine **82f** was achieved in line with previous synthesis in the group<sup>182</sup> and the crude imine was used in the nitro-Mannich reaction (**Scheme 158**). Reaction with 2-vinyl-*trans*- $\beta$ -nitrostyrene **64d** afforded the product  $\beta$ -nitroacetamide in good yield and excellent diastereoselectivity. Interestingly, the presence of the styrene moiety did not lead to a large reduction in yield, as seen in the formation of both  $\beta$ -nitroacetamides **102da** and **102ad**.



**Scheme 158.** Formation of  $\beta$ -nitroacetamide **102df** from glyoxylate imine **82f**

#### 2.3.5.2 Radical cyclisation of **102df**

Submission of  $\beta$ -nitroacetamide **102df** to the optimised denitration-cyclisation conditions resulted in successful cyclisation to give a complex mixture. A ratio of indane diastereomers 60:20:20 of **449** was observed from the methyl peak ratios at  $\delta$  1.02 ppm (3H, d,  $J$  = 7.0, 60 %), 1.13 ppm (3H, d,  $J$  = 7.0, 20 %) and 1.15 ppm (3H, d,  $J$  = 7.0, 20 %), with the presence of small underlying peaks. These peaks may correspond to a fourth isomer, or a fragmentation isomer. Analysis by MS found the molecular ion 436 ( $M + H^+$ ) and its ammonia adduct at 453 ( $M + \text{NH}_4^+$ ) as the only peaks, suggesting that the mixture contained indanes **449** and possibly trace amounts of fragmentation isomer(s).

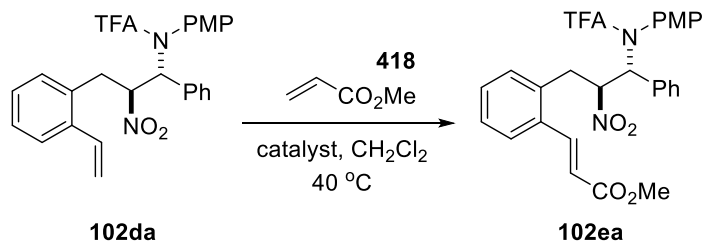


**Scheme 159.** Radical denitration-cyclisation of  $\beta$ -nitroacetamide **102df**

The fragmentation or 1,4-acetyl-transfer of C=O type fragments is known<sup>237</sup> via radical processes, however analysis by  $^{13}\text{C}$  NMR suggested that there were no peaks present that indicated the presence of a  $\text{CH}_2\text{N}$  group ( $\delta \sim 52$  ppm), in fact only  $\text{CHN}$ -type peaks  $\delta \sim 60$  ppm were observed. Analysis of the HSQC spectrum also showed no  $\text{CH}_2$  groups linked to a carbon atom  $\delta \sim 60$  ppm, these peaks corresponded to single  $\text{CHN}$  peaks as expected. Thus the presence of any fragmentation products was ruled out. It appears that addition to a carbonyl bond followed by  $\beta$ -scission of the C-CN bond is less favourable than addition to an aromatic ring, which is unsurprising due to the strength of the C=O bond, and its general inertness towards radical reactions.<sup>238</sup>

### 2.3.5.3 Derivatisation of $\beta$ -nitroacetamide **102da** – Olefin metathesis

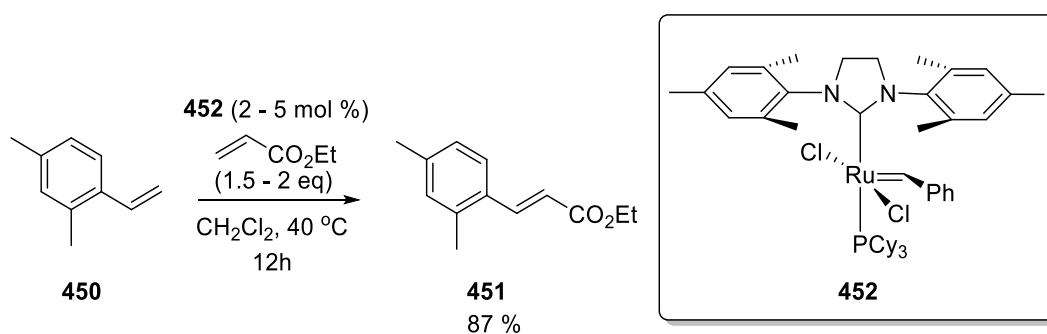
Although the formation of  $\beta$ -nitroacetamide **102da** via the nitro-Mannich reaction had proved low-yielding, its late-stage derivatisation was appealing, as synthesis of electron-poor nitroalkenes had previously proved challenging (**Table 19**). It was envisaged that derivatisation of the styryl tether would be carried out by olefin metathesis, and a range of alkenes could be used, in theory leading to a large array of electron-rich and electron-poor styryl tethers (**Scheme 160**).



**Scheme 160.** A late stage derivatisation by olefin metathesis

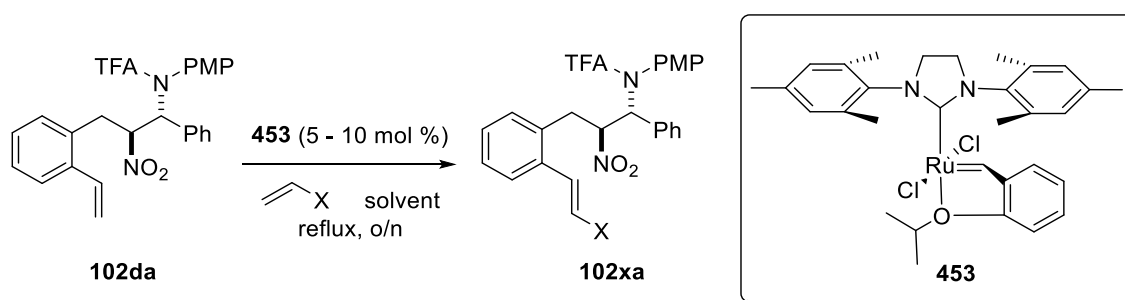
It was thought that the conditions required for olefin metathesis would be tolerated by the delicate  $\beta$ -nitroacetamides. A report by Grubbs<sup>239</sup> suggested that matching of specific reactivity types of alkenes and the correct catalyst could result in selective metathesis

reactions. Alkene cross-metathesis is known to be a capricious process due to the possibility of several different reactions occurring; the high reactivity of some alkenes can cause them to homodimerise, removing them from the reaction cycle (except in certain cases where secondary metathesis is possible). Alternatively, some alkenes may prove unreactive, and may require the use of more reactive catalysts. The design of the reaction is important, coupling alkenes of different reactivity types should lead to more selective cross-metathesis. A report of positive results for reactions between 2-substituted styrenes and acrylates using catalyst **452** led us to believe that this reaction may proceed with good yields under optimal conditions. An example is the reaction of 2,4-dimethylstyrene **450** with ethyl acrylate in  $\text{CH}_2\text{Cl}_2$  with **452**, which afforded **451** in very good yields (**Scheme 161**).<sup>239</sup>



**Scheme 161.** Grubbs metathesis of a type II styrene with ethyl acrylate

Due to the literature precedent for the reaction of the substituted styrene with ethyl acrylate, initial investigations of olefin metathesis of  $\beta$ -nitroacetamide **102da** were based on this reaction. Reaction of  $\beta$ -nitroacetamide **102da** with methyl acrylate **418** was carried out, using the Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst **453** which was readily available, in  $\text{CH}_2\text{Cl}_2$  using 2 eq alkene, as described by Grubbs.<sup>239</sup> TLC monitoring of the reaction using 2 eq methyl acrylate **418** showed significant amounts of starting material after 6 h, hence a second portion (2 eq) of **418** was added, before stirring o/n, leading to further consumption of starting material. Purification afforded the desired acrylate **102ea** in a reasonable 56 % yield (Entry 1, **Table 21**). An increase in equivalents of **418** to 10 and an increase in the catalyst loading from 5 – 10 mol % resulted in an essentially quantitative conversion by  $^1\text{H}$  NMR. A cleaner conversion was later achieved by reaction in neat methyl acrylate **418** with 10 mol % catalyst **453** in a sealed tube at 75 °C, giving an isolated yield of 82 % (Entry 2).

**Table 21.** Olefin metathesis of  $\beta$ -nitroacetamide **102da** to generate a range of styryl tethers

Entry	X	Alkene eq	453 mol %	% Yield <sup>d</sup>
<b>1</b> <sup>a</sup>	CO <sub>2</sub> Me ( <b>418</b> )	4	5	<b>102ea</b> (56)
<b>2</b> <sup>b,c</sup>	CO <sub>2</sub> Me ( <b>418</b> )	-	10	<b>102ea</b> (82)
<b>3</b> <sup>a</sup>	C <sub>6</sub> H <sub>5</sub> ( <b>454</b> )	2	5	<b>102ga</b> (54)
<b>4</b> <sup>a,c</sup>	C <sub>6</sub> H <sub>5</sub> ( <b>454</b> )	15	7.5	<b>102ga</b> (78)
<b>5</b> <sup>a</sup>	CN ( <b>335</b> )	2	5	-
<b>6</b> <sup>a</sup>	CH <sub>2</sub> TMS ( <b>455</b> )	4	5	<b>102ia</b> (39)
<b>7</b> <sup>a</sup>	COMe ( <b>456</b> )	2	5	-
<b>8</b> <sup>b,c</sup>	COMe ( <b>456</b> )	-	10	-
<b>9</b> <sup>a</sup>	CH <sub>2</sub> OTBS ( <b>457</b> )	10	5	-
<b>10</b> <sup>a,c</sup>	CH <sub>2</sub> OTBS ( <b>457</b> )	10	10	-
<b>11</b> <sup>a,c</sup>	B(Pin) ( <b>458</b> )	2	10	-
<b>12</b> <sup>b</sup>	OEt ( <b>459</b> )	-	5	-

<sup>a</sup> reaction run in CH<sub>2</sub>Cl<sub>2</sub> <sup>b</sup> reactions run neat <sup>c</sup> reactions performed in a sealed tube <sup>d</sup> Isolated yield

As limited solubility of the styryl  $\beta$ -nitroacetamide **102da** was generally observed in neat alkene solvent (with the exception of polar alkenes **418**, **456** and **459**), reaction of **102da** with a range of alkenes was run in CH<sub>2</sub>Cl<sub>2</sub>, with 2 eq alkene and 5 mol % catalyst **453**. Monitoring of the reaction by TLC or <sup>1</sup>H NMR allowed for the addition of extra catalyst **453** or alkene if conversion was low. To our delight, cross-metathesis of the styryl  $\beta$ -

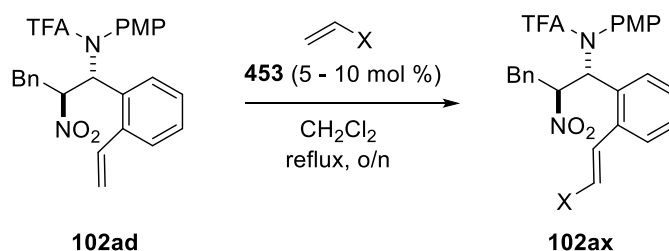


nitroacetamide **102da** with styrene **454** did not pose any problems, leading initially to a good yield (Entry 3). Increasing the equivalents of styrene (15 eq) and catalyst loading (7.5 mol %) and conducting the reaction on a scale > 1 mmol afforded **102ga** in a very good yield (Entry 4, **Table 21**). Olefin cross metathesis is often highly selective for the *E*-alkene; characterisation of acrylate **102ea** and the stilbene **102ga** by  $^1\text{H}$  NMR confirms the *E*-orientation ( $^3J_{\text{HH}} = \sim 16.0$  Hz = *E* orientation), with alkene peaks at 6.48 ppm (1H, d,  $J = 15.7$ ) and 8.08 ppm (1H, d,  $J = 15.7$ ) for the acrylate and 7.13 ppm (1H, d,  $J = 16.0$ ) and 7.48 ppm (1H, d,  $J = 16.0$ ) for the stilbene.

The use of vinyl methyl ketone **456**, acrylonitrile **335**, TBS-protected allyl alcohol **457** or allyl pinacol boronic ester **458** led to no product formation (Entries 5,7, 8-11). Reaction was attempted under different conditions, however this still led to no product. Allyl boronate esters are known to homodimerise quickly (Entry 11). In the case of the protected allylic alcohol **457**, only starting material was recovered under the conditions used. It was expected that methyl vinyl ketone **456** would prove an efficient coupling partner, however starting material was also recovered in this reaction. In the case of acrylonitrile **335**, it is known that its use can be problematic in cross-metathesis reactions with other  $\pi$ -conjugated alkenes due to the similar electronic properties of the alkenes.<sup>240</sup> Use of ethyl vinyl ether (**459**) also proved unsuccessful, with only a trace amount of product observed by  $^1\text{H}$  NMR (Entry 12). The use of allyl trimethylsilane **455** afforded product **102ia** in moderate yield (Entry 6) as a major and minor isomer. The major isomer was thought to be the *E*-isomer due to assignment of the  $^3J_{\text{HH}}$  across the alkene as 15.3 Hz. Assignment of the minor isomer was not possible due to overlap in the necessary areas of the spectrum. Attempts at varying the conditions did not lead to a higher yield of **102ia** or the ability to scale up the reaction, hence it was abandoned.

#### 2.3.5.4 Derivatisation of $\beta$ -nitroacetamide **102ad** – Olefin metathesis

With derivatives of  $\beta$ -nitroacetamide **102da** in hand, attention was turned to the derivatisation of  $\beta$ -nitroacetamide **102ad**. The initial focus of derivatisation was the use of olefin metathesis, although this reaction had proved capricious. Due to its success in the previous coupling with **102da**, methyl acrylate **418** was attempted for the first coupling reaction with styryl  $\beta$ -nitroacetamide **102ad** (**Table 22**)

**Table 22.** Olefin metathesis of  $\beta$ -nitroacetamide **102ad** to generate a range of styryl tethers

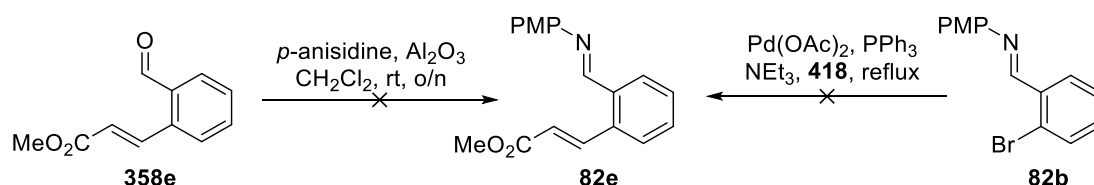
Entry	X	Alkene eq	453 mol %	% Yield <sup>d</sup>
<b>1<sup>b</sup></b>	CO <sub>2</sub> Me ( <b>418</b> )	-	7.5	-
<b>2<sup>a</sup></b>	CO <sub>2</sub> Me ( <b>418</b> )	20	10	-
<b>3<sup>a</sup></b>	C <sub>6</sub> H <sub>5</sub> ( <b>454</b> )	10	10	<b>102ag</b> (41)
<b>4<sup>a</sup></b>	CN ( <b>335</b> )	2	10	-
<b>5<sup>a</sup></b>	COMe ( <b>456</b> )	4	10	<b>102aj</b> (< 10)

<sup>a</sup>reaction run in CH<sub>2</sub>Cl<sub>2</sub> <sup>b</sup> reactions run neat <sup>c</sup> reactions performed in a sealed tube <sup>d</sup> Isolated yield

Cross-metathesis of  $\beta$ -nitroacetamide **102ad** was less successful. Surprisingly, no reaction of **102ad** with methyl acrylate was seen using the conditions which had previously given high yields (Entry 1, **Table 22**). Attempted reaction under other conditions also led to no formation of the desired product. As expected, reaction with acrylonitrile **335** gave no reaction (Entry 4). Unexpectedly, reaction with methyl vinyl ketone **456** led to the generation of small amounts of product (Entry 5), however it was abandoned due to the low yield. The only successful reaction was the coupling of  $\beta$ -nitroacetamide **102ad** with styrene, which led to isolation of the product **102ag** in a moderate yield (Entry 3). However this low yield, and problems with separation of the stilbene **102ag** from the parent styrene **102ad** meant even this reaction was of limited use. It was thought that subjection of the impure mixture of **102ag** to radical conditions would be unwise, as in addition to the variety of possible isomers formed from cyclisation of the desired radical precursor, a mixture of isomers from the parent alkene **102ad** would afford a more complex mixture and cause problems with purification. Hence a range of other methods were sought for the formation of derivatised  $\beta$ -nitroacetamide **102da** and **102ad** tethers in addition to the successful acrylate **102ea** and stilbene **102ga**.

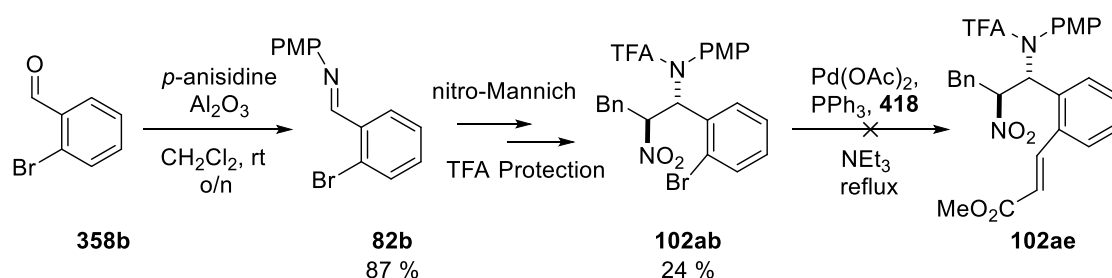
### 2.3.5.5 Other methods attempted to derivatise styryl $\beta$ -nitroacetamides **102da** and **102ad**

It was thought that a range of alternative methods for the generation of derivatives of  $\beta$ -nitroacetamides **102da** and **102ad** could be attempted. Previous work towards the generation of a nitroalkene containing a Michael acceptor was difficult due to the side-reactions possible with the highly electron poor acrylate group (**Table 19**). The formation of an imine from acrylate **358e** was attempted by the addition of *p*-anisidine in the usual way, this also proved unsuccessful, affording a complex mixture, which was not unexpected. A subsequent attempt to form imine **82e** centred on the Heck reaction<sup>217</sup> of 2-bromoimine **82b** with methyl acrylate **418**, unfortunately this was also unsuccessful, giving recovered starting material (**Scheme 162**).



**Scheme 162.** Attempted formation of imine **82e**

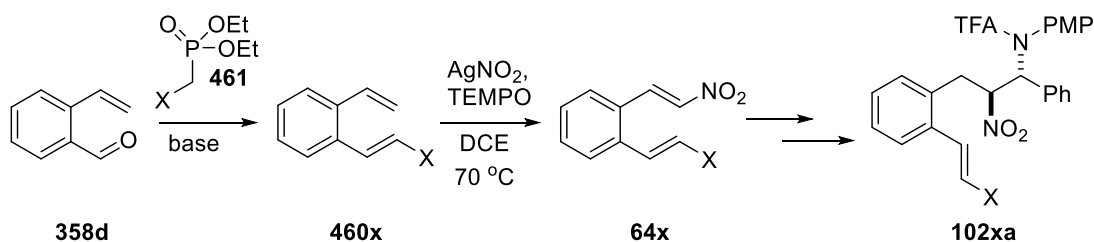
A further attempt at the Heck reaction for installation of the acrylate moiety late-stage was the reaction of the 2-bromophenyl- $\beta$ -nitroacetamide **102ab**, derived from the corresponding imine **82b**. Unfortunately,  $\beta$ -nitroacetamide **102ab** was obtained in an unoptimised yield of only 24 % yield. Heck reaction<sup>217</sup> of this substrate also proved unsuccessful due to the harsh conditions of the reaction (**Scheme 163**).



**Scheme 163.** Attempted Heck reaction of  $\beta$ -nitroacetamide **102ae**

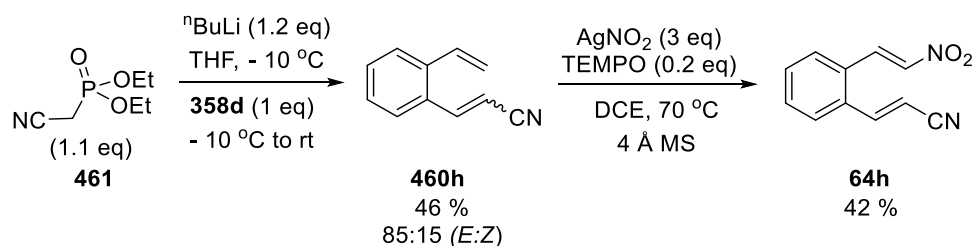
The possibility of formation of a nitroalkene **64x** via a new route was made possible after the discovery of a mild and stereoselective process for the nitration of alkenes by  $\text{AgNO}_2$  and TEMPO by Maity.<sup>241</sup> The formation of nitroalkenes directly from styrenes would negate the use of nucleophiles which could add into a Michael acceptor present in the molecule. The proposed reaction route would start from 2-vinylbenzaldehyde **358d**;

Wittig reaction would install the desired electron-poor alkene and nitration would give rise to the nitroalkene **64x** (**Scheme 164**). The reductive nitro-Mannich reaction would then be performed on nitrostyrene **64x** to give  $\beta$ -nitroacetamides **102xa**. In previous work in this group,<sup>58</sup> chemoselective nucleophilic addition of nucleophiles into ethyl 3-nitroacrylate had led to formation of the nitronate, which was trapped with an imine in the presence of acid (**Scheme 25**). By analogy it was hoped that chemoselective nucleophilic 1,4-addition into the more electron-poor nitroalkene would occur to form the nitronate. The nitronate could then be trapped in the subsequent nitro-Mannich step.



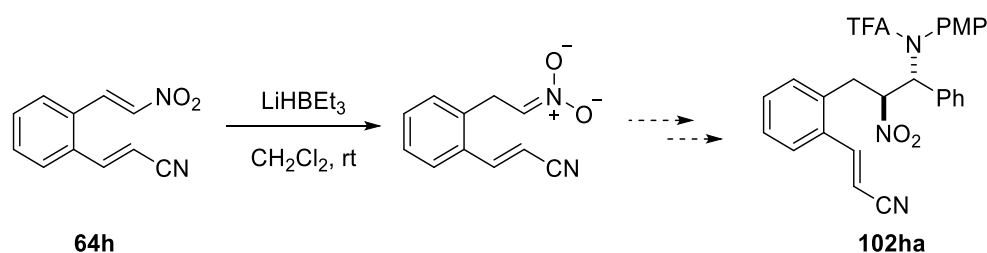
**Scheme 164.** Formation of nitroalkene with an inbuilt electron-poor alkene

Due to the inability to form acrylonitrile derivative **102ha** via olefin metathesis, initial investigations into the Horner-Wadsworth-Emmons reaction of aldehyde **358d** focussed on the formation of a cyano- derivative via reaction with diethylcyanophosphonate **461** in the presence of a base. Investigations commenced with the deprotonation of **461** with  $n\text{BuLi}$  at  $-78^\circ\text{C}$  in THF followed by the addition of aldehyde **358d** and stirring to rt o/n. Unfortunately low selectivity was observed, with an *E/Z* ratio of 65:35 of the product acrylonitrile **460h**. Iodine catalysed isomerisation of the alkene mixture was unsuccessful. From observation of the reaction, it was evident that the reaction became heterogeneous at  $-78^\circ\text{C}$ , which led to uncontrolled reaction of the phosphonate anion with the aldehyde on dissolution in the solvent as the temperature rose, giving lack of selectivity in the Horner-Wadsworth-Emmons reaction. It was hypothesised that addition of the aldehyde to the anion at a higher temperature would result in a more controlled reaction at a specific temperature and hopefully a higher selectivity. Reaction at  $0^\circ\text{C}$  led to a homogeneous reaction mixture and isolation of the product **460h** in 58 % yield with a slightly improved *E/Z* ratio of 75:25. Reaction at  $-10^\circ\text{C}$  afforded a further improved *E/Z* ratio of 85:15. Unfortunately, the isomers could not be separated by column chromatography, hence the mixture of isomers was submitted into the nitration reaction. It was hoped that separation of the nitroalkenes **64h** may prove more successful.



**Scheme 165.** Formation of nitro-Mannich precursor 2-acrylonitrile-nitrostyrene **64h**

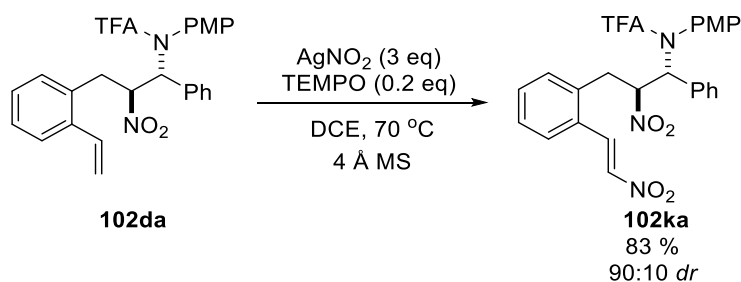
Nitration of the mixture of styrenes **460h** was successful using the conditions described by Maity,<sup>241</sup> with reduced loading of TEMPO (0.2 eq). This resulted in selective nitration of the styrene at the less hindered  $\beta$ -position of the alkene and with total control of selectivity, only the *E*-nitroalkene was observed as expected, with no nitration of the acrylonitrile. Gratifyingly, separation of the *E*- and *Z*-acrylonitrile nitroalkenes was possible, giving a moderate yield of 42 % of the desired product **64h** with *E*-geometry. The minor *Z*-isomer was obtained in 6 % yield. Characterisation of **64h** as the *E,E*-isomer was confirmed by  $^1\text{H}$  NMR with acrylonitrile peaks at  $\delta$  5.89 ppm (1H, d,  $J = 16.3$ ,  $\text{CHCN}$ ) and 7.75 ppm (1H, d,  $J = 16.3$ ,  $\text{CHCHCN}$ ), *E*-geometry of the alkene is given by the  $^3J_{\text{HH}}$  values of 16.3 Hz. The nitroalkene peaks at  $\delta$  7.48 (1H, d,  $J = 13.4$ ,  $\text{CHNO}_2$ ) and 8.27 (1H, d,  $J = 13.5$ ,  $\text{CHCHNO}_2$ ) confirm the *E*-geometry of the nitroalkene with  $^3J_{\text{HH}}$  values of  $\sim 13.5$ , typical of *E*-nitroalkenes. Heck reaction of 2-bromostyrene **419** with acrylonitrile under the previously successful conditions<sup>217</sup> for formation of methyl 2-(2-bromobenzyl)acrylate **358e** from 2-bromobenzaldehyde **358b** (Table 18) was also attempted to generate **460h**, however this reaction proved unsuccessful, giving recovered starting material. The *E*-isomer **64h** was subjected to the reductive nitro-Mannich reaction conditions to investigate the addition of Superhydride to the reaction mixture; no nitronate was formed, based on TLC analysis (visualisation of the nitroalkane on protonation of the nitronate)(Scheme 166). Quenching of the reaction (no addition of imine **82a**/acid-investigation addition of hydride only) showed a complex mixture of products by  $^1\text{H}$  NMR. Nitro-Mannich trapping of the intermediate nitronate was not attempted due to lack of material.



**Scheme 166.** Attempted nitro-Mannich reaction of **64h**

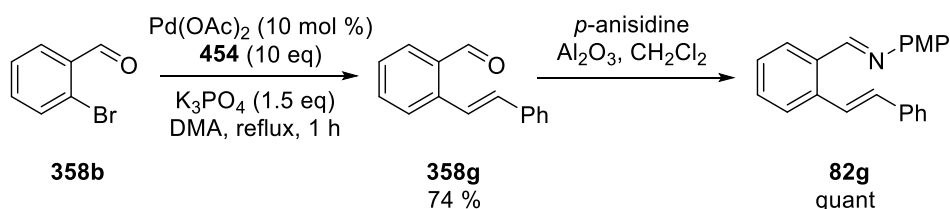
No alkenyl peaks were observed in the crude  $^1\text{H}$  NMR, however no expected products from single hydride addition into the nitroalkene or acrylonitrile were present. In addition, no peaks for addition of hydride into the nitroalkene followed by cyclisation on to the acrylonitrile group were observed. As the molecule contains two Michael acceptors which can undergo addition from any nucleophiles generated, a variety of intra- and inter-molecular reactions could take place. Purification did not afford any desired products. As nitroalkenes **64x** can undergo multiple reaction pathways on addition of Superhydride this route for the derivatisation of  $\beta$ -nitroacetamides **102xa** was abandoned.

Derivatisation of styryl  $\beta$ -nitroacetamide **102da** via the  $\text{AgNO}_2$ /TEMPO methodology described by Maity<sup>241</sup> to a pendant nitroalkene was hypothesised due to the mildness of the reaction conditions. Nitration of **102da** was successfully performed under these conditions to afford **102ka** in very good yield (**Scheme 167**). A mixture of isomers were formed (90:10 ratio) however analysis by  $^1\text{H}$  NMR suggested that this was not a mixture of *E*- and *Z*-isomers, due to the similarity of the  $^3J_{\text{HH}}$  values of the alkenyl protons (Major isomer  $^3J_{\text{HH}} = 13.4$  Hz, Minor isomer  $^3J_{\text{HH}} = 13.4$  Hz). It may be that some epimerisation of the  $\text{CHNO}_2$  proton has occurred during the reaction, leading to a slight drop in *dr* of  $> 95:5$  (*anti:syn*) of the parent  $\beta$ -nitroacetamide **102da** to 90:10 in the product **102ka**. The minor isomer cannot be assigned for the most part due to its underlying presence in the spectrum, it is thus tentatively assigned as the *syn*-isomer of **102ka**.



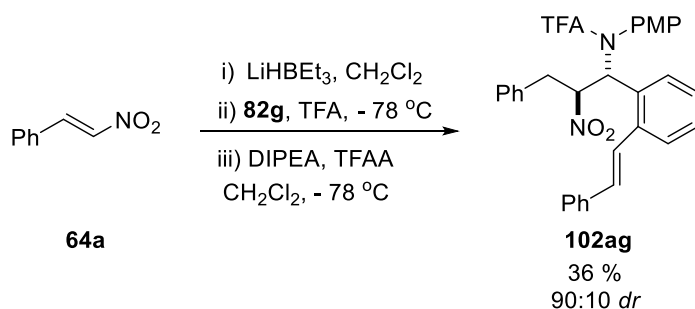
**Scheme 167.** Nitration of  $\beta$ -nitroacetamide **102da**

Derivatisation of  $\beta$ -nitroacetamide **102ad** via olefin metathesis had proved difficult, with the only successful reaction, the coupling of the parent alkene with styrene to give stilbene **102ag**, proving difficult to purify. Different methods for the derivatisation of the parent styrene **102ad** were therefore required. Due to the problems with purification of **102ag**, a new route for the generation of the stilbene derivative **102ag** via the nitro-Mannich reaction was envisaged. Although low yields of reactions of styryl-derived imine **102ad** was previously observed, the stilbene would not encounter the problems encountered by the electron-poor alkene imine synthesis. Aldehyde **358g** was generated via the Heck reaction of 2-bromobenzaldehyde **358b** with styrene (**Scheme 168**).<sup>242</sup> Subsequent condensation with *p*-anisidine under the usual conditions afforded the corresponding imine **82g** in quantitative yield.



**Scheme 168.** Formation of *N*-PMP stilbene imine **82g**

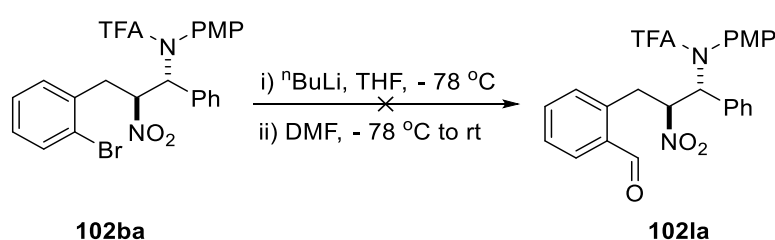
Nitro-Mannich reaction of *trans*- $\beta$ -nitrostyrene **64a** with imine **82g** afforded  $\beta$ -nitroacetamide **102ag** in moderate yield, and good *dr*. The moderate yield was in line with those observed for styryl derivatives **102da** and **102ad**. A lower yield of **102ag** was achieved using the nitro-Mannich reaction than via olefin metathesis (41 %), however purification of the nitro-Mannich reaction afforded pure **102ag**, which did not contain impurities of **102ad** which could not be removed after olefin metathesis.



**Scheme 169.** Nitro-Mannich reaction of *N*-PMP stilbene imine **82g**

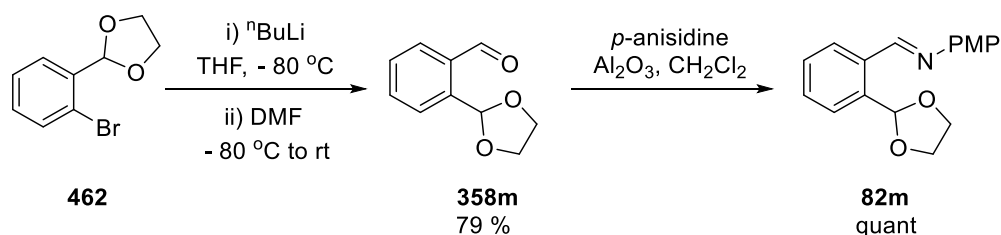
For the formation of electron-poor alkene derivatives of  $\beta$ -nitroacetamides **102da** and **102ad** another route was proposed. If a 2-formyl  $\beta$ -nitroacetamide **102la** could be

generated, derivatisation of the aldehyde could afford a range of new alkene derivatives **102xa** (*c.f.* **Scheme 164**). Protection of aldehydes as their acetal derivatives had enabled Luzzio to form a range of electron-poor alkenes post-Henry reaction.<sup>169</sup> It had originally been thought that the acetal may not survive the nitro-Mannich reaction due to the possible deprotection of the acetal *in situ* by TFA, leading to an exposed aldehyde. A halogen-lithium exchange-formylation reaction of  $\beta$ -nitroacetamide **102ba** was attempted in order to circumvent the longer synthesis and acetal protection required (**Scheme 170**). Unfortunately this reaction was unsuccessful, resulting in decomposition of **102ba** via elimination of TFA-NH-PMP **364**.



**Scheme 170.** Attempted formylation of  $\beta$ -nitroacetamide **102la**

Due to this lack of success in the direct formylation of 2-bromo- $\beta$ -nitroacetamide **102ba**, the acetal nitro-Mannich route was attempted. The generation of 2-(1,3-dioxolan-2-yl)benzaldehyde **358m** from 2-bromobenzaldehyde ethylene acetal **462** was carried out in very good yield via the formylation method previously described for the formation of 2-vinylbenzaldehyde, on a large scale (> 0.1 mol). This material was successfully subjected to imine formation, giving imine **82m** in quantitative yield.

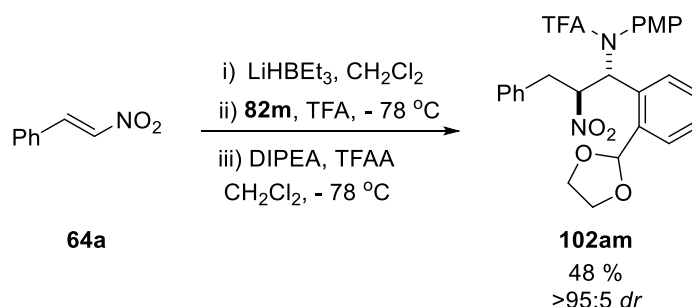


**Scheme 171.** Formation of acetal derived *N*-PMP imine **82m**

Imine **82m** was used *in situ* in the nitro-Mannich reaction with *trans*- $\beta$ -nitrostyrene **64a**, and afforded  $\beta$ -nitroacetamide **102am** in moderate yield (**Scheme 172**). Only one diastereoisomer was observed (> 95:5) and this is assigned as the *anti*-diastereoisomer in line with previous work in the group, and the general trend towards the *anti*-isomer in the nitro-Mannich reaction.<sup>4</sup> Only a trace amount (< 5 %) of an aldehyde peak at  $\delta$  10.4 ppm

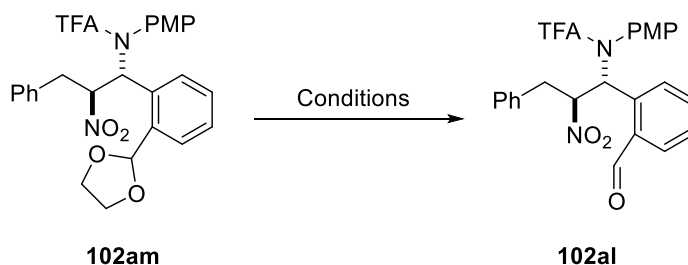


was observed in the nitro-Mannich crude  $^1\text{H}$  NMR, presumably due to de-acetalisation; it is possible that further aldehyde produced via de-acetalisation may have decomposed under the reaction conditions, however no significant by-products were observed.



**Scheme 172.** Nitro-Mannich reaction of imine **82m**

With  $\beta$ -nitroacetamide **102am** in hand, de-acetalisation was then attempted via several different methods. Stirring **102am** with *p*-toluenesulfonic acid in acetone at rt o/n resulted in 66 % conversion to the aldehyde **102al** by  $^1\text{H}$  NMR (Entry 1, **Table 23**). Reaction with  $\text{FeCl}_3/\text{SiO}_2$  in acetone at rt led to a very good yield (Entry 2). Attempted de-acetalisation of the non-TFA protected  $\beta$ -nitroamine by stirring in acetone with  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ <sup>243</sup> led to a complex mixture.



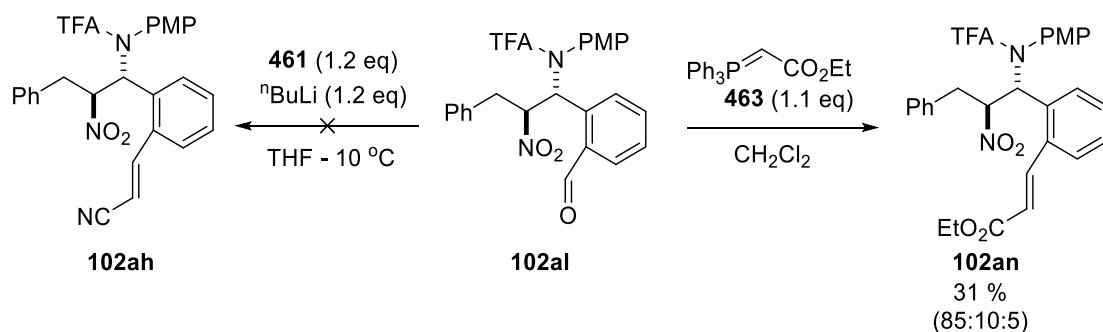
**Table 23.** De-acetalisation of **102am**

Entry	Conditions	% Yield <b>102al</b> <sup>a</sup>
1	<i>p</i> TSA, acetone, rt, o/n	66 <sup>b</sup>
2	$\text{FeCl}_3/\text{SiO}_2$ , acetone, 1 d	82

<sup>a</sup>Isolated yield <sup>b</sup>Conversion by  $^1\text{H}$  NMR

It was hypothesised that a variety of methods for the derivatisation of aldehyde **102al** could be used to generate alkenes for radical cyclisation. Firstly, Horner-Wadsworth-Emmons reaction of the aldehyde was attempted as previously described (**Scheme 165**) using the diethylcyanophosphonate anion **461** (1.2 eq), generated by deprotonation with  $^n\text{BuLi}$  (**Scheme 173**). Due to the similar  $\text{pK}_a$  values of the  $\text{CHNO}_2$  proton and the

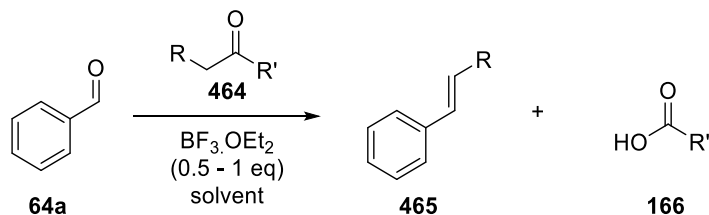
diethylcyanophosphonate (16-17), it had been suspected that deprotonation  $\alpha$ -to the nitro group may occur; degradation with recovery of TFA-NH-PMP **364** confirmed this suspicion. As this reaction was no longer feasible, alternative methods for alkene creation under milder conditions were sought. It was thought that the use of triphenylphosphorane-type Wittig reagents may be more successful due to their lower basicity; (carbethoxymethylene)triphenylphosphorane **463** has a  $pK_a \sim 8.5^{244}$  (vs nitro group  $\sim 16$ -17) and it was hoped that Wittig reaction would be favoured over deprotonation. Reaction of aldehyde **102al** with triphenylphosphorane **463** was indeed more successful, with isolation of a mixture of the (*E*)-ethyl acrylate **102an** and two minor isomers in a moderate yield (**Scheme 173**). It would appear that the two minor isomers contain the same molecular ion peak as the major isomer as analysis by MS shows only the parent molecular ion peak at 557 ( $M + H^+$ ) and the ammonia and sodium ion adducts at 574 ( $M + NH_4^+$ ) and 579 ( $M + Na^+$ ). Only (*E*)-ethyl acrylate **102an** could be assigned, with confirmation of the (*E*)-geometry of the alkene by  $^1H$  NMR ( $^3J_{HH} = 15.5$  Hz) from the alkenyl peak at  $\delta$  6.27 (1H, d,  $J = 15.5$  Hz,  $CHCO_2Et$ ) the other alkene peak could not be definitively assigned due to the complex nature of the  $^1H$  NMR spectrum. The minor isomers were observed by  $^1H$  NMR, with the benzylic peaks visible at  $\delta$  2.84 ppm (1H, *br* d,  $J = 14.4$ , 10 %) and 3.11 ppm (1H, dd,  $J = 14.7$ , 11.1, 10 %), and 2.76 ppm (1H, dd,  $J = 15.5$ , 2.6, 5 %) and 3.28 ppm (1H, dd,  $J = 15.1$ , 11.3, 5 %). It is likely that these isomers include the (*Z*)-alkene isomer and a product of epimerisation of the  $CHNO_2$  centre, to give trace amounts of the *syn*-diastereoisomer. Configuration of the alkene for both minor isomers could not be obtained due to overlap in the  $^1H$  NMR spectrum.



**Scheme 173.** Electron-poor alkene formation from aldehyde **102a**

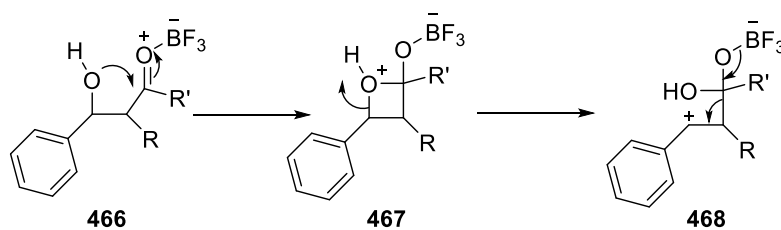
Another method for the derivatisation of aldehyde **102aI** was an interesting boron trifluoride initiated Aldol-Grob reaction reported by Kabalka.<sup>245</sup> The aldol reaction of aryl aldehydes or ketones with a ketone results in the formation of a  $\beta$ -hydroxycarbonyl **466** which then undergoes BF<sub>3</sub>-catalysed fragmentation, affording (*E*)-alkenes **465** and the

corresponding acid **166** (**Scheme 174**). It was hoped the non-basic conditions of the reaction would reduce the possibility of epimerisation of the acidic nitro centre.



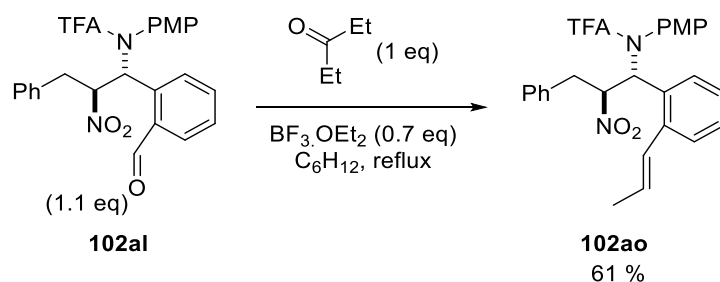
**Scheme 174.** Aldol-Grob reaction of aryl aldehydes to afford (*E*)-alkenes

The mechanism for the Grob rearrangement<sup>246</sup> of the  $\beta$ -hydroxycarbonyl intermediate **466** was proposed to proceed via formation of a four-membered lactol **467** followed by rearrangement to a stabilised benzylic cation **468**. Regeneration of the carbonyl leads to cleavage of the carbon-carbon bond, generating the alkene **465** (**Scheme 174 & 175**).<sup>245</sup>



**Scheme 175.** Proposed mechanism for the Grob rearrangement<sup>245</sup>

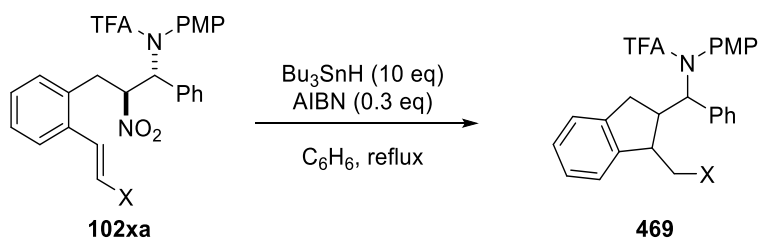
It was thought that this would prove an effective method for the generation of alkyl-substituted styrenes. Reaction of aldehyde **102al** with 3-pentanone was run at reflux in hexane, leading to successful formation of a simple methyl substituted (*E*)-styrene **102ao** in good yield (**Scheme 176**). The yield of 61 % for 3-pentanone reaction with **102al** matches the yield reported by Kabalka for reaction of 3-pentanone with 2-chlorobenzaldehyde. It was found that formation of electron rich styrenes in this reaction can lead to a lowering of the reaction yield from > 80 % to ~ 60 % yield due to polymerisation of the styrene under the reaction conditions.<sup>245</sup> Gratifyingly, it would appear that under these conditions, no epimerisation of the  $\text{CHNO}_2$  proton took place. Confirmation of the (*E*)-geometry of the alkene unfortunately could not be definitively confirmed by  $^1\text{H}$  NMR due to the overlap of adjacent signals in the  $^1\text{H}$  NMR, however in line with the exclusive formation of the (*E*)-alkene geometry by this method in the literature, **102ao** is also assigned as the (*E*)-alkene.

**Scheme 176.**  $\text{BF}_3 \cdot \text{OEt}_2$ -catalysed alkene formation of **102ao**

### 2.3.6 Radical cyclisation reactions of styryl tether derivatives

#### 2.3.6.1 Radical denitration of derivatives of styryl $\beta$ -nitroacetamide **102da**

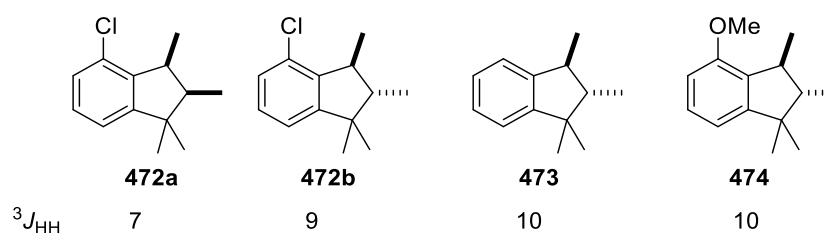
With a range of derivatives of the styryl tethered  $\beta$ -nitroacetamide **102da** in hand, radical cyclisation reactions were attempted under the optimised conditions.

**Table 24.** Radical denitration-cyclisation of derivatives of  $\beta$ -nitroacetamide **102da**

Entry	X	Product	% Yield <sup>a</sup>	<i>dr</i>
1	CO <sub>2</sub> Me ( <b>102ea</b> )	<p style="text-align: center;"><b>470</b></p>	59 31 <sup>b</sup> ( <b>470a</b> ) 11 <sup>b</sup> ( <b>470b</b> )	(40:40:20) <sup>c</sup> ( <i>cc:ct:tc</i> or <i>tt</i> )
2	Ph ( <b>102ga</b> )	<p style="text-align: center;"><b>471</b></p>	47 3 <sup>b</sup> ( <b>471a</b> )	(40:40:20) <sup>c</sup>
3	NO <sub>2</sub> ( <b>102ka</b> )	Complex mixture	-	-

<sup>a</sup> Combined Isolated yield of diastereoisomers <sup>b</sup> Isolated yield by recrystallization <sup>c</sup> Rough crude *dr*

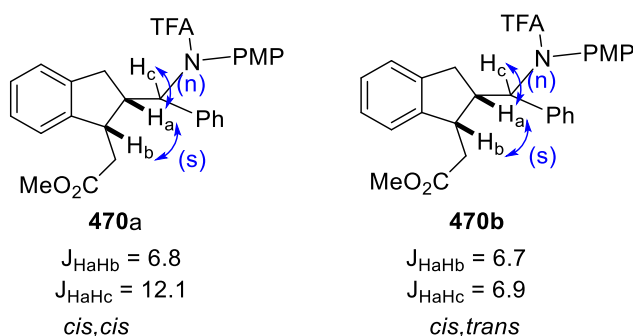
Methyl acrylate derivative **102ea** underwent radical denitration-cyclisation in good yield (Entry 1, **Table 24**). The crude *dr* obtained from the reaction mixture showed a mixture of three isomers with a ratio 40:40:20. As for the previous cyclisation reactions, a possible four diastereoisomers could be produced in the reaction with orientations *cis,cis(cc)*-, *cis,trans(ct)*-, *trans,cis(tc)*- or *trans,trans(tt)*- across the indane ring ( $H_aH_b$ , **Fig. 19**) and between the ring and acetamide ( $H_aH_c$ ). Purification by column chromatography proved insufficient for isolation of the individual diastereoisomers, with mixtures of isomers isolated. The mixtures of isomers were recrystallized from  $CH_2Cl_2$ /Hexanes, affording pure samples of the two main isomers in 31 % and 11 % yield. Full characterisation of both compounds **470** was undertaken, with confirmation of the molecular ion peaks at 498 ( $M + H^+$ ) and 497 ( $M^+$ ) by MS analysis of **470a** and **470b**. The indane ring was confirmed as before, using  $^1H$  NMR and  $^{13}C$  techniques, HSQC and HMBC providing the structural information necessary to assign in particular the relevant protons  $H_a$  and  $H_b$  for analysis of the stereochemistry of each isomer. As previously described, the stereochemistry of substituted indanes may be tentatively assigned by a range of  $^3J_{HH}$  coupling data (compared to known values) and NOE data comparing the interactions through space (as s/m/w/n – strong/medium/weak/no interaction); the chemical shifts of important protons can also be used as indicators of the local environment. As described, *trans,cis*-2-amino indane **437b**, exhibited a  $^3J_{HH}$  coupling of 6.9 Hz for *cis*-protons. Literature values<sup>247</sup> for similar alkyl-substituted indanes (**Fig. 18**) also give a similar value of 7 Hz for *cis*-1,2-substituted indane **472a**; the *trans*-couplings are much higher, ~ 9-10 Hz, similar to those observed for *trans*-coupling in the 2-aminoindanes **437** (8.7 – 9.2 Hz) (**Fig. 17**).



**Fig. 18.**  $^3J_{HH}$  values for some *cis*- or *trans*-1,2-alkyl-substituted indanes

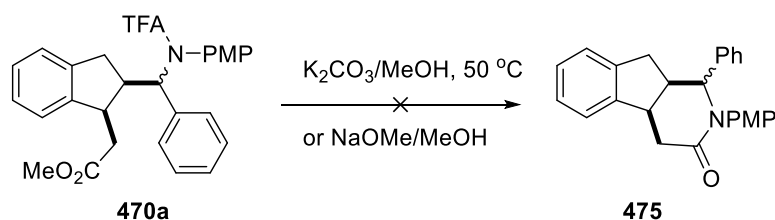
The relative orientations ( $H_aH_b$ ) of **470a** and **470b** were assigned as *cis*- due to a number of compelling data. Firstly,  $^3J_{HaHb} = 6.8$  and 6.7 Hz for **470a** and **470b** respectively (**Fig. 19**), suggesting the same ring junction orientation in both isomers and a probable *cis* relationship  $H_a-H_b$  in agreement with literature values<sup>234a, 247</sup> and previous assignment of

**437 (Scheme 153).** The possibility of a *cis*-relationship of the indane substituents in both rings was further supported by strong (s) NOESY interactions between protons  $H_a$ - $H_b$  in both isomers. Unfortunately the relationship between protons  $H_a$ - $H_c$  was more ambiguous due to free rotation about the C-CN bond.



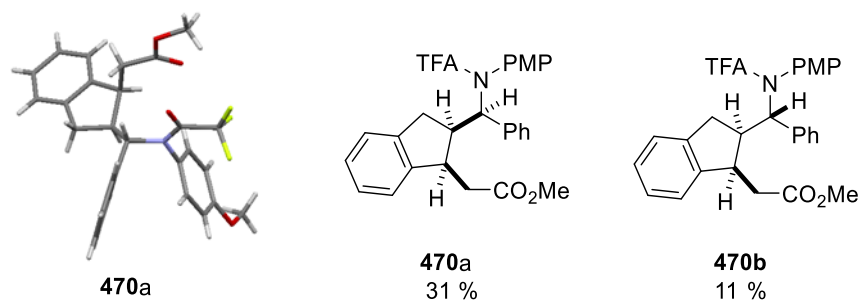
**Fig. 19.** Stereochemical assignment of the isolated isomers of **470** showing through-space NOE interactions

Attempted TFA deprotection of **470a** proved unsuccessful using  $K_2CO_3/MeOH$ <sup>65</sup> or  $NaOMe/MeOH$ . It was hoped that lactamisation of the free NHPMP with the ester would occur *in situ*, affording lactam **475**, from which the relative stereochemistry of the acetamide could be ascertained (**Scheme 177**).



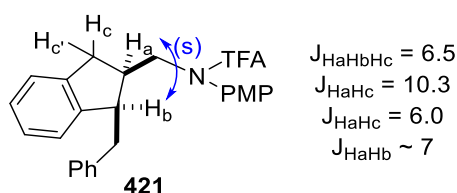
**Scheme 177.** Attempted TFA deprotection for lactam formation

Fortunately, diastereoisomer **470a** was obtained as a crystalline solid, and a crystal structure of the molecule was obtained (**Fig. 20**). The *cis*-configuration of diastereoisomer **470a** was confirmed, and the orientation of protons  $H_a$ - $H_c$  was confirmed as a *cis*-relationship (as drawn). As the *cis,cis*-orientation of **470a** was confirmed, and a similar *cis*-orientation across the indane ring was indicated by  $^3J_{HaHb} = 6.7$  Hz for **470b**, it was assigned as the *cis,trans*-isomer (**Fig. 20**).



**Fig. 20.** Crystal structure of **470a** and relative analysis of **470b**

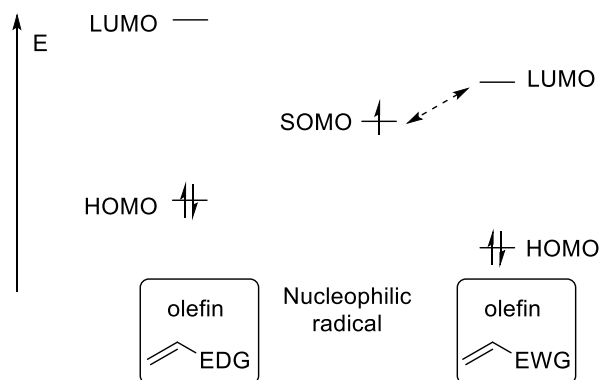
The crystal structure of **470a** allowed for the corresponding tentative assignment of values in the range  $^3J_{\text{HaHb}} \sim 7$  Hz as *cis*-H<sub>a</sub>-H<sub>b</sub> relative stereochemistry when obtained for similarly 1,2-dialkyl-substituted indane molecules. This strengthened the argument for the *trans,cis*-assignment of acetamide-substituted indane ring **437b**, in which  $^3J_{\text{HbHc}} = 6.7$  Hz, with larger *trans*-indane ring couplings  $^3J_{\text{HH}} \sim 8.7 - 9.2$  Hz. It also supports the assignment of rearrangement product **421** (Scheme 149) as the *cis*-isomer. In addition to strong interactions (s) H<sub>a</sub>-H<sub>b</sub>, rearrangement product **421** displays a  $^3J_{\text{HaHb}}$  value of  $\sim 7$  Hz, a value in the range of a *cis*-substituted indane (Fig. 21).



**Fig. 21.** Stereochemical assignment of **421** influenced by **470a** assignment

Reaction of stilbene-derived  $\beta$ -nitroacetamide **102ga** under the same conditions resulted in the successful denitration-cyclisation reaction to afford indane **471** (Entry 2, Table 24) with an identical crude ratio of diastereoisomers (40:40:20) as that observed for the methyl acrylate derivative **470**. Purification yielded a mixture of diastereoisomers in 47 % combined yield; recrystallization afforded pure **471a**, although in very low yield. The second major isomer **471b** was not isolated pure, however a rough picture of the major indyl-ring shifts could be ascertained. The relative stereochemistry of **471a** was assigned as *cis*-H<sub>a</sub>-H<sub>b</sub>, as  $^3J_{\text{HH}} = 6.6$  Hz, in analogy with the confirmed  $^3J_{\text{HH}}$  value of 6.6 Hz. NOESY interactions could not be distinguished due to similar chemical shifts overlapping. The relative stereochemistry across the C-CN bond was not determined and unfortunately a crystal structure of **471a** could not be obtained. Analysis of isomer **471b**

showed that interestingly, the  $^3J_{\text{HH}}$  values across the ring were all very similar. Benzylic peaks at  $\delta$  2.65 ppm (1H, dd,  $J = 13.2, 7.2$ ) and 2.70 ppm (1H, dd,  $J = 13.3, 7.2$ ), and 3.00 ppm (1H, d,  $J = 16.1$ ) and 3.24 ppm (1H, dd,  $J = 16.1, 7.2$ ) all corresponded with a signal at  $\delta$  2.88 ppm (2H, apt t,  $J = 7.2$ ) which appeared to place the CH protons equivalent, with equivalent  $^3J_{\text{HH}}$  coupling values to the adjacent ‘seen’ protons. The  $^3J_{\text{HaHb}} = 7.2$  Hz, suggesting a *cis*-relationship across the indane ring; this would align with the observation of the *cis*-indane isomers **470a** and **470b** as forming the majority (80 %) of the stereochemical ratio. The isomers **471a** and **471b** were thus assigned as the *cis,cis*- and *cis,trans*- isomers together, however neither isomer was definitively assigned. The minor isomer (20%) would therefore be assigned as either the *trans,cis*- or *trans,trans*- diastereoisomer. A higher yield of indane **470** than indane **471** was observed, this is due to more favourable cyclisation of the intermediate radical in acrylate **102ea** than stilbene **102ga**. This is explained by frontier molecular orbital (FMO) effects; the radical derived from denitration of  $\beta$ -nitroacetamides has a relatively high energy SOMO, with nucleophilic character. The nucleophilic SOMO is closer in energy to the low-energy LUMO of the electron-poor alkene than the more electron rich HOMO of the stilbene, leading to more favourable orbital interaction between the SOMO and LUMO of the acrylate and a faster rate of cyclisation (**Fig. 22**). Electron-rich alkenes such as stilbene would have more favourable orbital overlap with an electron-poor radical.<sup>164a</sup>



**Fig. 22.** A qualitative description of the FMO interactions of nucleophilic and electrophilic radicals

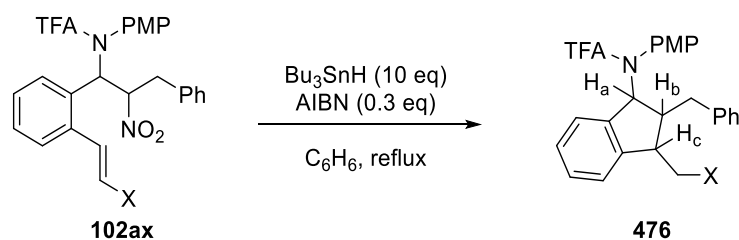
Radical denitration-cyclisation of the nitrostyryl  $\beta$ -nitroacetamide **102ka** unfortunately led to a complex mixture, and no isolation of any indane product. It is likely that decomposition occurs via several pathways, due to the sensitivity of the compound. Under the reaction conditions, the  $\text{sp}^2$  primary nitro group would not be expected to undergo



denitration by reaction with TBTH, however other radical pathways could compete with reduction of the secondary nitro group in the molecule.<sup>248</sup>

### 2.3.6.2 Radical denitration of derivatives of styryl $\beta$ -nitroacetamide **102ad**

With the successful radical denitration-cyclisation reactions of methyl acrylate **102ea** and stilbene **102ga**, attention was shifted to the cyclisation of the imino-tethered cyclisations of  $\beta$ -nitroacetamides **102ad**. Stilbene-tethered  $\beta$ -nitroacetamide **102ag** was subjected to the radical conditions described (**Table 25**), and pleasingly led to successful denitration-cyclisation, affording the product indane **477** in moderate yield and as an inseparable mixture of diastereoisomers (Entry 1, **Table 25**). Full characterisation of the inseparable diastereoisomers **477** was possible (see appendices: section 4.3 for correlation tables). Assignment of the major and minor diastereoisomers was conducted by  $^1\text{H}$  NMR, using  $^3J_{\text{HH}}$  coupling values and NOESY interactions. Analysis of  $J$  couplings showed that for the major diastereoisomer **477a**  $^3J_{\text{HaHb}} = 7.1$  Hz,  $^3J_{\text{HbHc}} = \sim 7$  Hz, suggesting a common orientation of protons  $\text{H}_a\text{-H}_b$  to  $\text{H}_b\text{-H}_c$  in the *cis*-region as previously described. However NOESY correlations show  $\text{H}_a\text{-H}_b$  (w),  $\text{H}_b\text{-H}_c$  (w) and  $\text{H}_a\text{-H}_c$  (m), suggesting a *trans,trans*-configuration. This diastereoisomer demonstrates the difficulty in assignment of indanes, and the requirement for multi-faceted evidence for assignment. The minor isomer **477b** was tentatively assigned as the *trans,cis*-isomer, with a large  $^3J_{\text{HaHb}} = 9.2$  Hz, which suggests a *trans*-orientation of these protons, further corroborated by weak NOESY interaction. The orientation of protons  $\text{H}_b\text{-H}_c$  was assigned as *cis*- due to the strong NOESY interaction between  $\text{H}_b\text{-H}_c$  and also due to a lack of interaction between protons  $\text{H}_a\text{-H}_c$ ,  $^3J_{\text{HbHc}} = 7.5$  Hz. The  $\text{CHN}$   $^1\text{H}$  NMR shifts of both protons  $\text{H}_a$  were also very similar to each other ( $\delta$  6.31 (**477a**), 6.28 ppm (**477b**)) and to those of **437a** ( $\delta$  6.28 ppm) and **437b**, ( $\delta$  6.24 ppm) suggesting little change in environment between  $\text{H}_a\text{-H}_b$  in all four molecules (*trans*-).

**Table 25.** Radical denitration-cyclisation of derivatives of  $\beta$ -nitroacetamide **102ad**

Entry	X	Product	% Yield <sup>a</sup>	<i>dr</i>
1	Ph ( <b>102ag</b> )	<p style="text-align: center;"><b>477</b></p>	34	60:40 ( <i>tt:tc</i> ) <sup>b</sup>
2	Me ( <b>102ao</b> )	<p style="text-align: center;"><b>478</b></p>	12 4 ( <b>478a</b> )	(70:30) <sup>c</sup> (95:5)

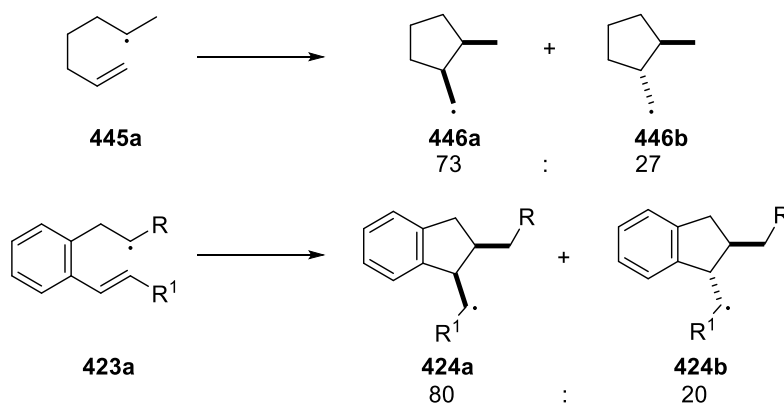
<sup>a</sup> Combined Isolated yield of diastereoisomers <sup>b</sup>Crude ratio <sup>c</sup>ratio of isolated diastereoisomers

Radical cyclisation of the (*E*)-methylstyrene derivative **102ao** was successful however the reaction was low-yielding, with only 12 % yield **478** isolated (Entry 2, **Table 25**). The *dr* of the crude reaction could not be measured due to the presence of tin residues in the crude; however the isolated material contained a *dr* of 70:30, with trace amounts of a possible third diastereoisomer. Further purification gave the major diastereoisomer in 95:5 *dr* albeit at a yield of only 4 %, however full characterisation was made. Analysis of the stereochemistry by NOESY interactions gave correlation between protons H<sub>a</sub>-H<sub>b</sub> (w), H<sub>b</sub>-H<sub>c</sub> (w) and H<sub>a</sub>-H<sub>c</sub> (s) suggesting a *trans,trans*-orientation. Analysis of <sup>3</sup>J<sub>HH</sub> couplings showed similar low couplings to those observed in **471b**, in this case <sup>3</sup>J<sub>HaHb</sub> = 7.6, <sup>3</sup>J<sub>HbHc</sub> = ~ 7.1 Hz (**478a**), in the range of observed values for *cis*-dialkyl substituted indanes. However the similar values across H<sub>a</sub>-H<sub>b</sub>, H<sub>b</sub>-H<sub>c</sub> suggest a *trans,trans*-environment due to the similar <sup>3</sup>J<sub>HH</sub> values suggesting a similar dihedral angle across both bonds. The chemical shift of the CHN proton (H<sub>a</sub>, δ 6.30 ppm) is also close to those of **437** (δ 6.28, 6.24 ppm) and **477** (δ 6.31, 6.28 ppm) suggesting a similar *trans*-H<sub>a</sub>H<sub>b</sub> environment. The relative stereochemistry was therefore tentatively assigned as *trans,trans*- due to the

consideration of all three pieces of data. The reason for the low yield of indane **478** is not clear, however the reaction was run on a small scale and separation from the TBTH residues was difficult, hence it is likely that some of the product was lost during partitioning of the product between hexanes/MeCN.

### 2.3.6.3 Stereoselectivity in the cyclisation of radical precursors **102xa**

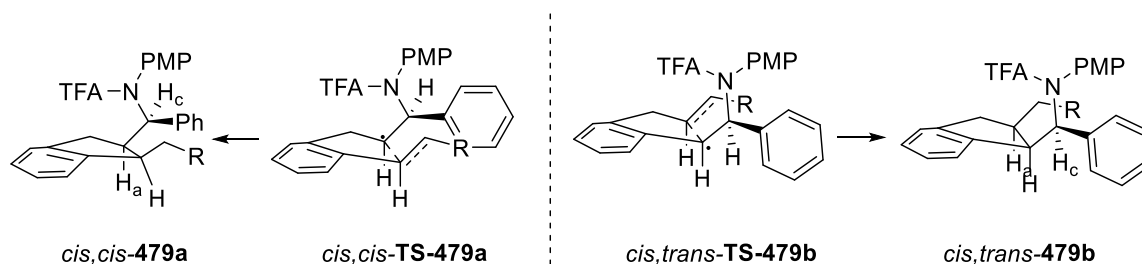
Initial investigations of cyclisation of unsubstituted styryl  $\beta$ -nitroacetamide **102da** led to the isolation of three expected indane products and a rearrangement product in the respective ratio (30:15:30:25) (**Table 20**). The (*E*)-substitution of the styrene tether with an ester or aromatic group led to the isolation of a majority of *cis*-substituted indane diastereoisomers, with a total of 80 % *cis*-isomer for indane **470** and a tentatively assigned 80 % of *cis*-substituted indane **471**. As previously described, *cis*-ring junction formation of 5-hexen-1-yl radical cyclisation is well documented, with the probability of deviation towards *trans*-ring junction increasing with increasing steric bulk of the 1-substituent. Cyclisation of 6-hepten-2-yl radical **445a** is known to proceed with a *cis:trans* ratio 73:27,<sup>172</sup> which resembles the ratio observed for the cyclisation of styryl  $\beta$ -nitroacetamide derivative **423a** where  $R^1 = \text{CO}_2\text{Et}$ , and may also be the case for  $R^1 = \text{Ph}$ . The minor (*trans*-) isomer in both cases was not isolated.



**Scheme 178.** *cis*-ring junction formation of 1-substituted 5-hexen-1-yl radicals

It would appear that under these conditions, no stereochemical induction was afforded from the  $\alpha$ -chiral centre to the radical. The *cis:trans* relationship was 50:50, giving an overall stereochemical ratio across three chiral centres of 40:40:20:0. Interestingly, only one *trans*-ring indane was formed, however it was not known whether this was the *trans,cis*- or *trans,trans*-diastereoisomer. The stereochemical ratio of the *cis*- or *trans*-relationship  $\text{H}_a\text{-H}_c$  results from the population of diastereomeric transition states **TS-479a**

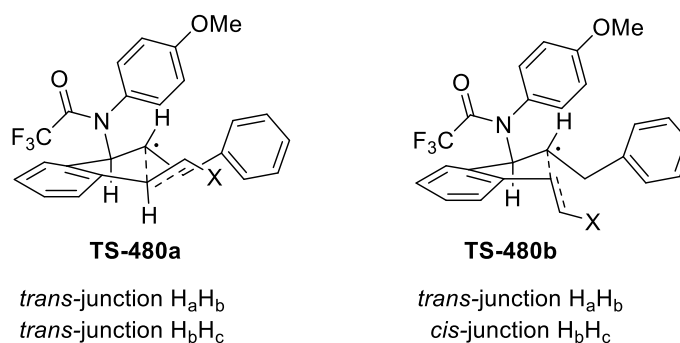
and **TS-479b** (Scheme 179). Although reasonable to very good diastereomeric induction may be observed in conformationally rigid molecules with an  $\alpha$ -chiral centre to the radical, the *exo*-C-CN bond can rotate easily, and gives little preference for one diastereomeric transition state over the other. This led to the isolation of the *cis,cis*- and *cis,trans*- products in equal quantities. This is not the case for  $\beta$ -nitroacetamides **102ax** which contain the acetamide chiral centre on the styryl chain, which has a strong effect on stereochemical induction in the transition state.



**Scheme 179.** Diastereomeric transition states accounting for the stereochemistry across the C-CN bond

#### 2.3.6.4 Stereoselectivity in the cyclisation of radical precursors **102ax**

The stereoselectivity of cyclisation of substituted styryl  $\beta$ -nitroacetamides **102ax** was previously discussed (see section 2.3.4.2) as highly influenced by the presence of the TFA-NH-PMP moiety on the styryl tether (Scheme 156). Placement of the trifluoroacetamide in the *pseudo*-equatorial position is thought to be highly favoured over its *pseudo*-axial alternative due to the large steric bulk of the *N*-TFA and *N*-PMP protecting groups, and this led to *trans,trans*- and *trans,cis*-**437** as the sole diastereoisomers observed (Scheme 156). The additional (*E*)-substitution of the styryl alkene increased the steric bulk of the alkene, and it was thought that this could lead to the increased favourability of either the *trans,trans*- or *trans,cis*-isomers. From the observed ratios of diastereoisomers, a higher proportion of the *trans,trans*-diastereoisomer was observed on substitution of the styrene by a phenyl ring (X = Ph, 60:40, *tt:tc*) and a methyl group (X = Me, 70:30, *tt:tc*). It would appear that *pseudo*-equatorial placement of the alkene is favoured (**TS-480a**) when increasing the bulk of X (Fig. 23). It may be that the conjugated phenyl ring adopts a planar conformation in which steric interactions with the benzyl group are minimised, with the slightly more sterically bulky methyl group resulting in the greatest increase in proportion of the *tt:tc* ratio from the original unsubstituted styrene (55:45 *tt:tc*).

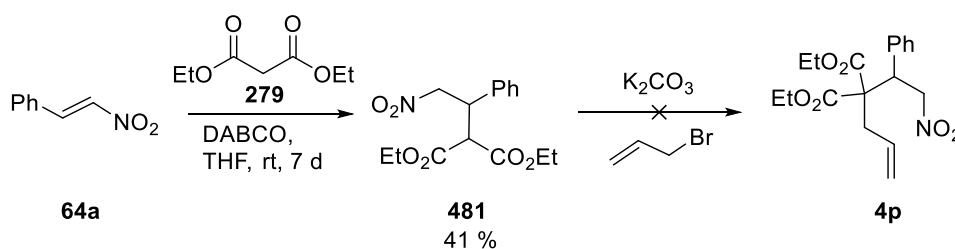


**Fig. 23.** Transition states for the formation of diastereoisomers from substituted styryl tethers

### 2.3.7 Development of hexenyl-based radical precursors

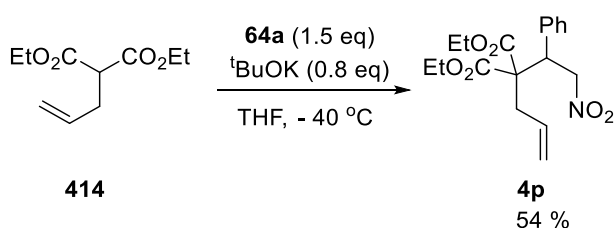
#### 2.3.7.1 *gem*-3,3-difunctionalised hexen-1-yl tethers

With the success of radical denitration-cyclisation of the styryl tethers and their derivatives, a series of alternative, non-planar tethers was investigated. As previously mentioned, the presence of *gem*-dimethyl substituents placed on various positions of the 5-hexen-1-yl radical resulted in an increased rate of cyclisation due to the influence of the *gem*-dimethyl substituents on the conformation of the alkyl chain (**Table 17**). The synthesis of differentially substituted 5-hexenyl tethers for incorporation into  $\beta$ -nitroacetamides was undertaken. Firstly the synthesis of a *gem*-diester tether was attempted. Synthesis of Michael adduct **481** via DABCO-catalysed addition of diethyl malonate **279** to *trans*- $\beta$ -nitrostyrene **64a** gave the desired product in moderate yield (**Scheme 180**).<sup>249</sup> Unfortunately, subsequent allylation failed, due to the formation of complex mixtures under the reaction conditions. Long reaction times at rt or high temperatures afforded complex mixtures, and short reaction times at rt gave mainly recovered starting material, using K<sub>2</sub>CO<sub>3</sub>/allyl bromide. The complex mixture is likely due to the number of possible products that may be formed via deprotonation at the malonate (pK<sub>a</sub> ~18-19)<sup>250</sup> or  $\alpha$ -nitro positions (pK<sub>a</sub> ~ 17).<sup>251</sup> In addition,  $\beta$ -elimination of the diethylmalonate from the nitronate is possible.



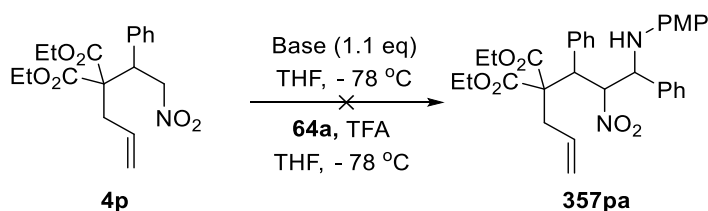
**Scheme 180.** Formation of *gem*-dimethyl nitroalkane **4p**

Previous work towards the synthesis of aldehyde **358c** (**Scheme 142**) had required the formation of diethyl 2-allylmalonate **414** on large scale. It was thought that 1,4-addition of the substituted malonate to *trans*- $\beta$ -nitrostyrene would result in the formation of nitroalkane **482** for subjection to the deprotonative nitro-Mannich reaction. Conjugate addition of diethyl 2-allylmalonate **414** (2.5 eq) to *trans*- $\beta$ -nitrostyrene **64a** (1 eq) using catalytic DABCO (0.2 eq)<sup>249</sup> in THF resulted in the isolation of **4p**, however only moderate yields (33 – 39 %) were achieved even at reflux. An alternative procedure reported by Kamimura<sup>252</sup> using <sup>t</sup>BuOK at low temperature was more successful, affording **4p** in good yield (**Scheme 181**).



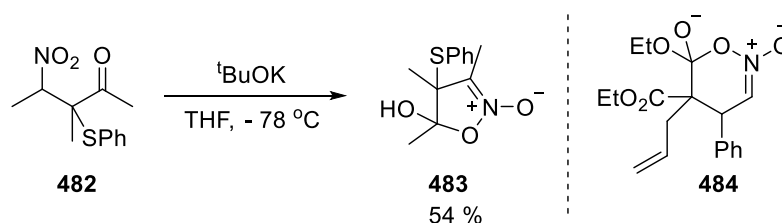
**Scheme 181.** 1,4-addition of allyl diethyl malonate to *trans*- $\beta$ -nitrostyrene

With nitroalkane **4p** in hand, a nitro-Mannich reaction was attempted (**Scheme 182**). Initial investigation of the nitro-Mannich reaction used bulky LDA as base, to avoid reaction with the *gem*-diester functional groups. Reaction of LDA was unsuccessful, resulting in the recovery of starting nitroalkane.



**Scheme 182.** Attempted nitro-Mannich reaction of nitroalkane **4p**

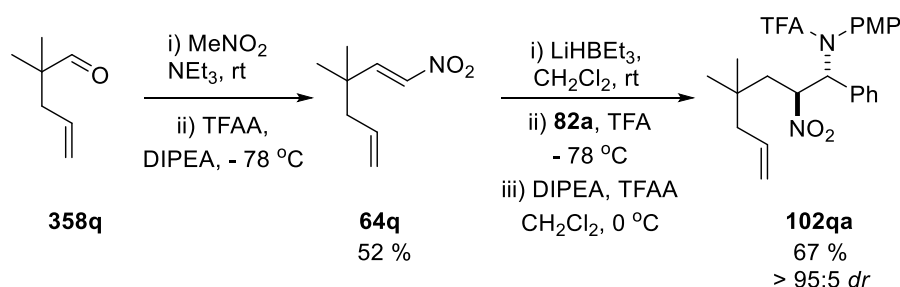
Use of a stronger base proved unsuccessful, with <sup>n</sup>BuLi and <sup>s</sup>BuLi both giving recovered starting material. Interestingly, only a trace amount of possible nucleophilic addition of the *n*-butyl group to the ester was observed in the crude material. The lack of nucleophilic addition to the imine suggests that the <sup>n</sup>BuLi is not present on addition of the imine. It is possible that deprotonation at the nitro position occurs to form a stabilised, unreactive nitronate anion **484**. The *O*-alkylation of nitronates via intramolecular cyclisation with ketones at the C-4 position is known (**Scheme 183**).<sup>74, 253</sup>



**Scheme 183.** Intramolecular *O*-Alkylation of a nitronate

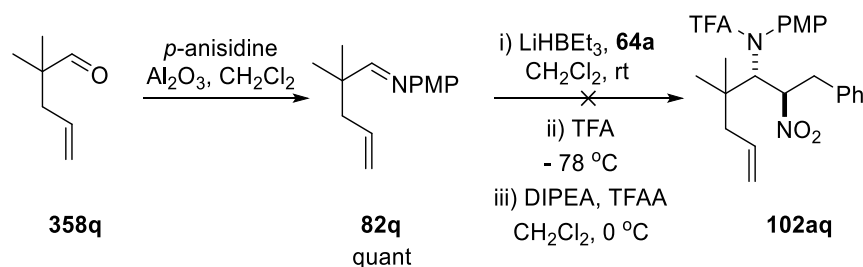
The use of secondary nitronates results in the isolation of the stable cyclic nitronate **483** in good yield; primary nitronates afford recovered starting material, which may involve collapse of the cyclic structure with re-protonation of the intermediate at the nitro position.<sup>253</sup> A similar report by the Anderson group of the double deprotonation of diethyl malonate adduct **481** (**Scheme 180**) followed by attempted nitro-Mannich reaction also proved unsuccessful.<sup>66a</sup>

With the lack of success for the nitro-Mannich reaction of nitroalkane **4p**, attempted formation of the *gem*-dimethyl variant was thought to be a more viable alternative. Aldehyde **358q** was commercially available, and nitroalkene formation proved successful, affording **64q** in good yield (**Scheme 184**). Subsequent nitro-Mannich reaction with imine **82a** afforded the corresponding  $\beta$ -nitroacetamide **102qa** in very good yield and excellent diastereoselectivity, assigned as the *anti*-diastereoisomer in line with previous work.<sup>62</sup>



**Scheme 184.** Formation of 3,3-*gem*-dimethyl hex-5-en-1-yl tethered  $\beta$ -nitroacetamide **102qa**

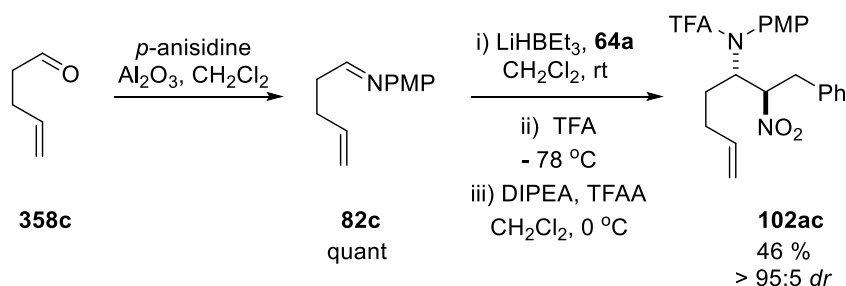
Unfortunately the corresponding imine **82q** derived from aldehyde **358q** did not undergo a successful nitro-Mannich reaction. This is thought to be due to the increased steric bulk afforded to the imine by the *gem*-dimethyl group adjacent to the imine.



**Scheme 185.** Attempted formation of  $\beta$ -nitroacetamide **102aq**

### 2.3.7.2 Mono-5-substituted hexen-1-yl tethers

Although the reaction of the unsubstituted hexenyl-tethered  $\beta$ -nitroacetamide **102ca** originally formed had proved unsuccessful, it was hypothesised that the equivalent amine-substituted hexenyl tethered  $\beta$ -nitroacetamide **102ac** may prove more successful due to the *gem*-dimethyl effect. Mono-substituted carbon chains do not induce such a strong effect as *gem*-disubstituted carbon centres, however the increase in cyclisation rate expected may increase the rate of cyclisation to a rate at which radical cyclisation of the tether occurs (*cf.* hydrogen abstraction or decomposition). Imine formation from aldehyde **358c** proceeded successfully, and immediate subjection of the crude imine to the nitro-Mannich reaction afforded  $\beta$ -nitroacetamide **102ac** in a reasonable yield and excellent diastereoselectivity (**Scheme 186**).

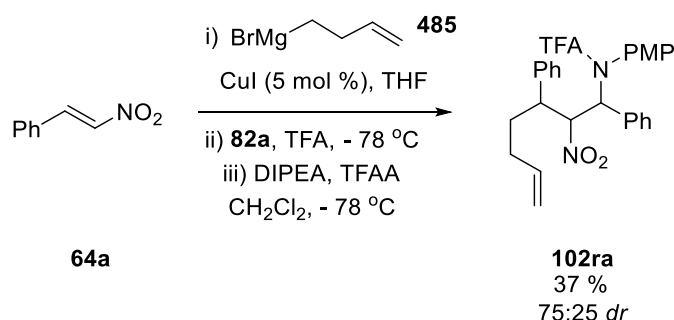


**Scheme 186.** Formation of  $\beta$ -nitroacetamide **102ac**

The same principle of mono-substitution of the hexenyl tether was investigated further by 5-substitution of the original hexenyl tether with a benzene ring. It was thought that this could be achieved via copper-catalysed 1,4-conjugate addition and *in situ* nitro-Mannich reaction of the nitronate generated. This has been demonstrated in the Anderson group, mainly with the addition of dialkyl zinc reagents to various nitroalkenes,<sup>55, 58, 60-61</sup> however the variation of dialkyl zinc reagents had proved less successful.<sup>60</sup> It was thought that simple installation of the alkene tether via copper-catalysed addition of a Grignard reagent may prove successful. Formation of homoallyl magnesium bromide **485** was



successful from 4-bromobut-1-ene, and addition of 1.5 eq **485** to *trans*- $\beta$ -nitrostyrene **64a** (1 eq) in the presence of 5 mol % CuI followed by trapping of the nitronate with imine **82a** gave the crude nitroamine as a mixture of isomers. Previous work has shown that judicious choice of solvent (leading to a heterogeneous or homogeneous reaction) can lead to a change in diastereoselectivity of the reaction (**Scheme 23**).<sup>55, 58, 60, 66a</sup> In this case (**Scheme 187**), three diastereoisomers could be observed in the reaction mixture, however the complex mixture of the <sup>1</sup>H NMR made it impossible to accurately label these as the *syn,syn*-, *syn,anti*-, *anti,syn*- or *anti,anti*- diastereoisomers by their <sup>3</sup>J<sub>HH</sub> couplings as had previously been used in this group. The ratio of diastereoisomers was 55:23:23 (A:B:C),<sup>254</sup> however on TFA protection of the  $\beta$ -nitroamines,  $\beta$ -nitroacetamide **102ra** were formed in 37 % yield, and a *dr* of 75:25 (A:B). This suggested that the third diastereoisomer (C) did not undergo TFA protection, and was not isolated as a trifluoroacetamide. In addition, a change in the diastereomeric ratio of the product  $\beta$ -nitroacetamides **102ra** suggests a loss of material of the second diastereoisomer (B) as the ratio A:B has changed from a twofold excess (55:23) to a threefold excess of A (75:25).



**Scheme 187.** Grignard addition to *trans*- $\beta$ -nitrostyrene followed by nitro-Mannich reaction

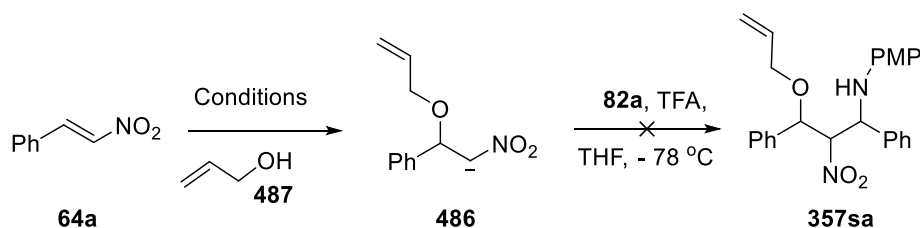
From these observations it is likely that the diastereoisomer which did not undergo TFA protection is the *syn,syn*-diastereoisomer, which is known to be more stable than the *anti*-isomers, and resistant to TFA-protection.<sup>55</sup> Similar work observed the *syn,anti*-diastereoisomer as the kinetic product in THF, and tentatively assigned the *anti,syn*-isomer as the third likely diastereoisomer due to its slightly higher stability than the *anti,anti*-product.<sup>55</sup> However this selectivity was dependent on the presence of zinc (II) trifluoroacetate dissolved in the reaction and explained by its ability to form a Zimmerman-Traxler type chair transition state (**Scheme 24**).<sup>55</sup> In this case, the major isolated trifluoroacetamide (A) may be the *syn,anti*- diastereoisomer and the minor isomer

is also tentatively assigned as the *anti,syn*-diastereomer, both of which can undergo TFA-protection.<sup>55</sup> Although the yield is only moderate, this is across three steps, and the *syn,syn*-diastereoisomer was not isolated, hence the actual yield of all three  $\beta$ -nitroamines would have been higher.

### 2.3.7.3 Heteroatom-substituted hex-5-en-1-yl tethers

Further derivatisation of the alkene tether focussed on the incorporation of heteroatoms into the chain. The presence of heteroatoms (O,N) in the chain results in an increased rate and regioselectivity of cyclisation resulting from better orbital overlap in the 5-*exo* transition state.<sup>165</sup> The effect is pronounced for an oxygen tether, leading to a 35-fold increase in rate on substitution of C-3 with an oxygen atom (Entry 1 vs 6, **Table 17**), this is compared to a 21-fold increase in rate on C-3 *gem*-dimethyl substitution (Entry 4, **Table 17**).

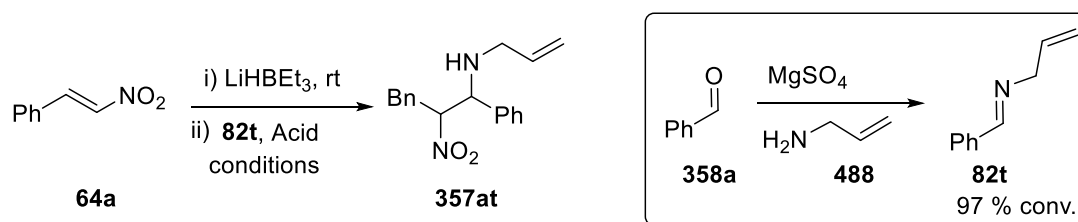
Attempted formation of an allyl tether focussed on the addition of allyl alcohol **487** to *trans*- $\beta$ -nitrostyrene **64a** followed by *in situ* nitro-Mannich reaction with imine **82a** (**Scheme 188**). Addition of the sodium salt of allyl alcohol generated from NaH followed by trapping with imine **82a** led to a mixture of starting materials. A melt of **64a** with allyl alcohol **487** to form the Michael adduct gave no reaction, and the addition of freshly prepared sodium allyl alkoxide in allyl alcohol (generated with sodium metal) gave a complex mixture of products which proved difficult to separate.



**Scheme 188.** Attempted formation of allyl alcohol-based tethered  $\beta$ -nitroamine **357sa**

Formation of an 'N'-substituted tether proved more successful; it was thought that using an *N*-allyl protecting group (*c.f.* *N*-PMP) would obviate C-3-substitution of the 5-hexenyl tether. Formation of *N*-allyl imine **82t** was achieved, and the crude imine used *in situ*, in a reductive nitro-Mannich reaction with *trans*- $\beta$ -nitrostyrene **64a** under the general conditions used for the formation of  $\beta$ -nitroacetamides (General procedure F). Screening reaction conditions resulted in a good conversion but very low *dr* in favour of *syn*- $\beta$ -nitroamine **357at** (Entries 1-2, **Table 26**). Switching to an AcOH quench in  $\text{CH}_2\text{Cl}_2/\text{THF}$

increased the *dr* slightly in favour of the *anti*-isomer (Entries 3-4) however the use of a larger equivalent of imine **82t** and acid (Entries 5-6) resulted in a higher *dr* and very good yield. The modified general procedure (Entry 6) was scaled up, and followed by TFA-protection, affording the corresponding  $\beta$ -nitroacetamide **102at** in 39 % yield, with a slightly reduced *dr* (75:25), it appeared that some decomposition occurred on TFA protection.



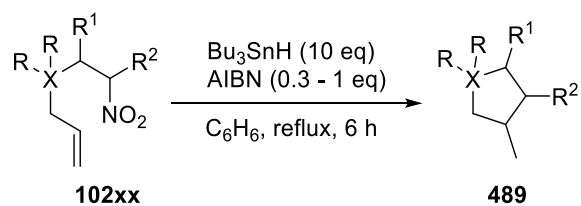
**Table 26.** Formation of *N*-allyl  $\beta$ -nitroamine **357at**

Entry	<b>82t</b> eq	Acid (eq)	solvent	Temp/ °C (time)	% Conv <sup>a</sup>	<i>dr</i> ( <i>anti</i> : <i>syn</i> ) <sup>b</sup>
<b>1</b>	1.13	TFA (1.14)	CH <sub>2</sub> Cl <sub>2</sub>	-78 (2h) rt (3h)	66	35:65
<b>2</b>	1.13	TFA (1.14)	CH <sub>2</sub> Cl <sub>2</sub>	-78 (1h) rt (1h)	62	35:65
<b>3</b>	1.13	AcOH (1.14)	CH <sub>2</sub> Cl <sub>2</sub>	-78 (1h) rt (1h)	47	60:40
<b>4</b>	1.13	AcOH (1.14)	THF	-78 (1h) rt (1h)	46	70:30
<b>5</b>	2	AcOH (3.5)	THF	-78 (1h) rt (1h)	75	85:15
<b>6</b>	2	TFA (3.5)	CH <sub>2</sub> Cl <sub>2</sub>	-78 (2h)	87	85:15

<sup>a</sup> from <sup>1</sup>H NMR <sup>b</sup> from <sup>1</sup>H NMR and comparison with lit. data for *anti*/*syn*

### 2.3.8 Radical cyclisation of hexenyl-based radical precursors

With three successful hexenyl-based  $\beta$ -nitroacetamide radical precursors formed, they were subjected to the radical denitration conditions (**Table 27**).

**Table 27.** Cyclisation of hexenyl derived tethers **102xx**

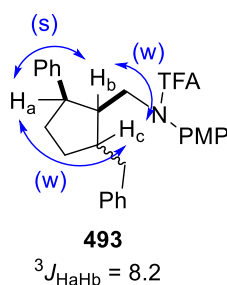
Entry	$\beta$ -nitroacetamide	Major Product	Minor Product
1	<p style="text-align: center;"><b>102qa</b></p>	<p style="text-align: center;"><b>490</b> 46 % (40:30:30<sup>a</sup> <i>dr</i>)</p>	<p style="text-align: center;"><b>491</b> 9 %</p>
2	<p style="text-align: center;"><b>102ac</b></p>	Complex mixture	-
3	<p style="text-align: center;"><b>102ra</b></p>	<p style="text-align: center;"><b>492</b> 24 % (40:35:25)</p>	<p style="text-align: center;"><b>493</b> 3 %</p>
4	<p style="text-align: center;"><b>102at</b></p>	<p style="text-align: center;"><b>494</b> 12 % (50:30:15:5)</p>	-

<sup>a</sup>Possible trace of a 4<sup>th</sup> diastereoisomer, could not confirm

Radical cyclisation of the *gem*-dimethyl substituted hexenyl  $\beta$ -nitroacetamide **102qa** proceeded with good yield (Entry 1, **Table 27**). The major product was the expected 5-*exo*-trig product, indane **490**, which was isolated as a mixture of diastereoisomers with an approximate 40:30:30 *dr*. In addition, a minor product was obtained, fragmentation isomer **491**. Assignment of the methyl cyclopentane isomers **490** was not possible due to the complex nature of the  $^1\text{H}$  NMR spectrum, however three diastereoisomers were observed. It may be that the fragmentation product **491** originated from a fourth isomer in which the methyl radical intermediate was held close to the benzene ring. Alternatively, the fragmentation isomer could have formed in the same way from either of the three isomers **490**, in competition with hydrogen abstraction from TBTH. The relative stereochemistry of the ring junction of the fragmentation isomer **491** could not be definitively determined, as the  $^3J_{\text{H}_a\text{H}_b}$  values could not be obtained. Analysis of through space interactions showed a (m-s) correlation  $\text{H}_a\text{-H}_b$ , it is possible this isomer may be *cis*-, however it is unassigned due to the complex nature of assignment of cyclopentane rings. The combined yield of products **490**, & **491**, 55 %, is similar to that of the styryl tether **102da**, and shows the positive effect of the *gem*-dimethyl group on the rate of cyclisation. Interestingly, the proportion of fragmentation is lower than that of the styryl tethered  $\beta$ -nitroacetamide **102da**. The flattening of the styryl transition state by the presence of the phenyl ring may have placed the indanyl methyl radical intermediate in closer proximity to the translocating phenyl ring (see **Scheme 149**) than the cyclopentyl methyl radical, leading to a higher proportion of fragmentation of the indanyl methyl radical than the cyclopentyl methyl radical (**Fig. 25**). Radical precursor **102ac** unfortunately led to a complex mixture of products including recovered starting material (Entry 2, **Table 27**). Only trace amounts of cyclisation and protodenitration was observed, hence purification was not undertaken. It would appear that radical denitration did not readily occur in this molecule, and that cyclisation was not significantly aided by the presence of the CHN stereocentre on the hexenyl tether.

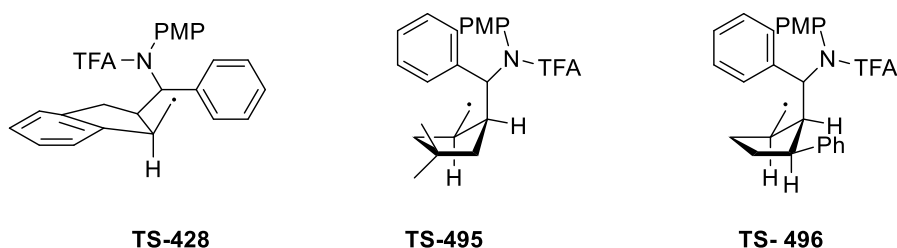
Radical cyclisation of  $\beta$ -nitroacetamide **102ra** proved successful, with a combined yield of 27 % (Entry 3, **Table 27**). The stereochemistry of the radical precursor diastereoisomers were attributed to the *syn,anti*- and *anti,syn*-diastereoisomers **102ra**, affording the substituents at C-1 and C-3 a fixed *anti*-conformation. This meant that although cyclisation would give products with 4 chiral centres, only a possible 4 diastereoisomers could be formed, due to the fixed relative orientation of C-1 and C-3.

Some 1,4-phenyl ring translocation was observed, however the yield of fragmentation product **493** was low. Hypothesised intermediate transition states for 1,4-phenyl translocation are shown in **Fig. 25**; a flattened indane-type transition state **TS-428** may place the methyl radical in closer proximity to the benzene ring than the envelope-type cyclopentyl methyl radical transition states **TS-495** and **TS-496**. Investigation of the stereochemistry of **493** suggested a *cis*-relationship between  $H_a$ - $H_b$  (**Fig. 24**) due to the strong NOE interaction  $H_a$ - $H_b$  (s). The relative orientation of  $H_c$  was less certain as weak interactions were seen for both  $H_b$ - $H_c$  (w), suggesting a *trans*-configuration and  $H_a$ - $H_c$  (w), suggesting  $H_a$  and  $H_c$  are on the same face of the cyclopentane ring, which would suggest a *cis,cis*-conformation.



**Fig. 24.** Through space interactions and  $^3J_{HH}$  couplings of **493**

A *cis*-orientation of  $H_a$ - $H_b$  would be unfavourable, due to the placement of a bulky substituent in a *pseudo*-axial position, however fragmentation may be from a minor isomer, in which the two major isomers formed are in a more favourable *trans*-orientation across  $H_a$ - $H_b$ , placing the bulky substituents in *pseudo*-equatorial positions. The transition states **TS-495** and **TS-496** are shown as the *cis*-isomers, however it is unclear from assignment of products **491** or **493** whether the *cis*- or *trans*-ring junction was formed. From earlier assignment of the indanyl fragmentation isomer **421** as *cis*- $H_aH_b$  and the propensity of 6-hepten-2-yl radicals to cyclise with *cis*-selectivity<sup>172</sup> (**Scheme 178**), this seemed a viable proposition. It was likely that holding the substituents on the cyclopentane ring in a *cis*-configuration would hold the methyl radical in closer proximity to the phenyl ring.



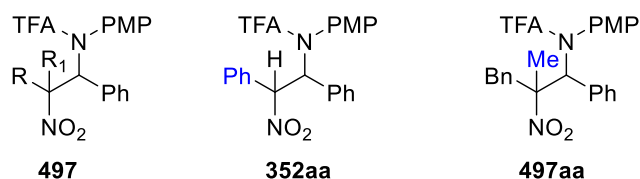
**Fig. 25.** Possible transition states for the translocation of the benzene ring

Subjecting  $\beta$ -nitroacetamide **102at** to radical denitration-cyclisation resulted in the formation of TFA-protected pyrrolidine **494** in low yield, as a complex inseparable mixture of all four possible diastereoisomers (50:30:15:5, A:B:C:D) (Entry 4, **Table 27**). It appeared that cyclisation of the 2-Ph-3-*N*-substituted-5-hexen-1-yl radical tether favoured the formation of two diastereoisomers A & B, with minor amounts of less favourable diastereoisomers C & D. It was not possible to discern the orientation of the substituents. The low yield may be partly due to the small scale of the reaction, with loss of material during work-up when removing residual TBTH. Characterisation of the pyrrolidine ring was limited due to the complex nature of the  $^1\text{H}$  NMR spectrum, however characterisation by mass spectrometry confirmed the desired molecular ion at 438 ( $M + \text{H}^+$ ). An attempted radical cyclisation of the non-TFA protected  $\beta$ -nitroamine equivalent **357at** was also attempted, however this gave a complex mixture of products and decomposition.

### 2.3.9 Attempted formation of 3° & activated 2° radical precursors

#### 2.3.9.1 Overview

The radical denitration of secondary nitro compounds is a difficult process and requires a large excess of TBTH in order to achieve reasonable yields,<sup>145</sup> due to difficulty in cleavage of the C-N bond (see section 1.4). Radical denitration is much more favourable upon stabilisation of the carbon radical to be formed by further substitution or replacement of an alkyl group ( $R, R^1$ , **Fig. 26**) by an adjacent electron-stabilising group<sup>146</sup> (e.g.  $\text{CO}_2R/\text{Ar}/\text{OR}$ ). It was proposed that radical denitration of  $\beta$ -nitroacetamides containing a tertiary or activated secondary nitro position (**Fig. 26**) would be more favourable and that this should improve yields and could allow for a reduction in the equivalents of TBTH used. Methods for the formation of tertiary  $\beta$ -nitroacetamides ( $R = R^1 \neq \text{H}$  (**497**)) included alkylation of the nitro position and nitro-Mannich reaction of a tri-substituted alkene. Alternatively, activated secondary  $\beta$ -nitroacetamides of type **497** where  $R = \text{Ar}$  (**352aa**) or  $\text{CO}_2R$  could be obtained via the deprotonative nitro-Mannich reaction.<sup>5</sup>

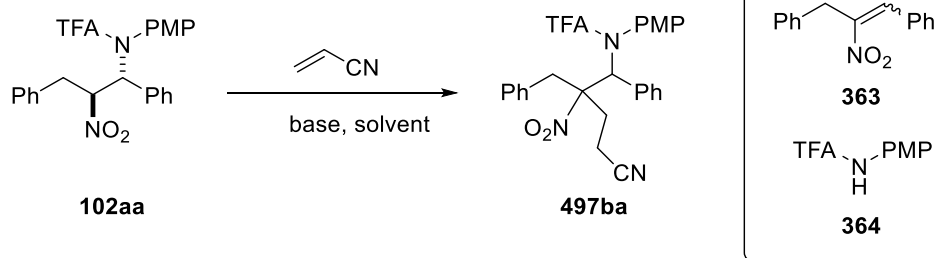


**Fig. 26.** Stabilisation of the  $\beta$ -nitro position to aid denitration

### 2.3.9.2 Attempted formation of tertiary $\beta$ -nitroacetamides

Primary investigations into the formation of tertiary  $\beta$ -nitroacetamides **497** focussed on the modification of secondary  $\beta$ -nitroacetamides **102** by alkylation of the nitro position. Previous work towards the Nef reaction (see section 2.2.2.2) had shown that deprotonation of the nitro group resulted in the elimination of the adjacent trifluoroacetamide **364**, forming nitroalkene **363**, and further products from subsequent reaction of the nitroalkene **363** (**Scheme 121**). Although this was the case across a range of basic Nef conditions, various conditions were screened in the hope of finding conditions in which alkylation predominated, with reduced elimination. Alkylation via 1,4-conjugate addition of  $\beta$ -nitroacetamide **102aa** to acrylonitrile **335** catalysed by various bases under different conditions was attempted (**Table 28**), however no alkylation product **497ba** was observed under any conditions. A melt between acrylonitrile and **102aa** proved unsuccessful, giving recovered starting material (Entry 1, **Table 28**). Starting material and small amounts of TFA-NH-PMP **364** and nitroalkene **363** were observed on reaction of **102aa** with acrylonitrile in the presence of basic alumina (Entry 2, **Table 28**). The use of DBU (1 eq) in MeCN (up to  $-40\text{ }^{\circ}\text{C}$ , run in THF below this temperature) resulted in 100 % conversion of the starting material to elimination products **363** and **364**. At lower temperatures, less degradation of the nitroalkene **363** occurred, allowing for equal recovery (Entries 3 – 7). The use of LDA as a base followed by copper-catalysed addition to the acrylonitrile gave a mixture of starting material and elimination products (Entry 8).



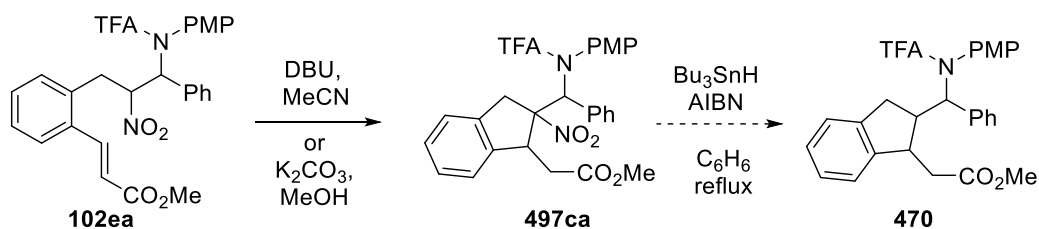
**Table 28.** Attempted alkylation via 1,4-conjugate addition to acrylonitrile

Entry <sup>a</sup>	Alkene eq	Base (eq)	Solvent	Temp/ °C	102aa:363:364
<b>1</b>	140	-	Neat	50	100:0:0
<b>2</b>	140	Al <sub>2</sub> O <sub>3</sub> (*)	Neat	rt	70:15:15
<b>3</b>	1.5	DBU (1)	MeCN	rt	0:30:70
<b>4</b>	1.5	DBU (1)	MeCN	0	0:25:75
<b>5</b>	1.5	DBU (1)	MeCN	- 40	0:35:65
<b>6</b>	1.5	DBU (1)	THF	- 78 to rt	0:50:50
<b>7</b>	1.5	DBU (1)	THF	- 78	0:50:50
<b>8</b>	1.5	LDA (1.1)/Cu <sup>b</sup>	THF	- 78	50:25:25

\*1 g per mmol <sup>a</sup>50 mg scale, 0.11 mmol <sup>b</sup>20 mol % CuI used

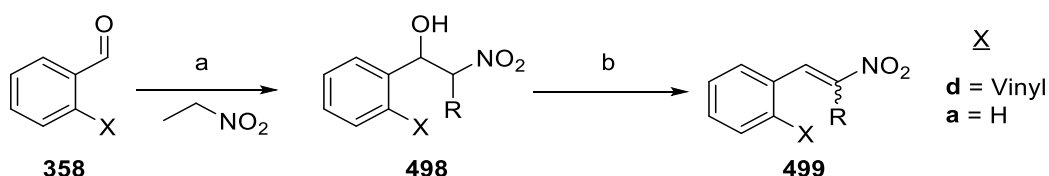
An intramolecular alkylation (cyclisation) of secondary β-nitroacetamide **102ea** was also attempted (**Scheme 189**). It was thought that formation of the cyclic tertiary β-nitroacetamide **497ca** would then allow for higher yields in the subsequent radical denitration step. Stirring **102ea** with DBU<sup>255</sup> (0.5 eq)/MeCN at rt led to a 75:25 ratio of elimination of TFA-NH-PMP **364** to cyclisation product **497ca**; reducing the temperature to - 20 °C gave no change in the elimination:cyclisation ratio, however use of K<sub>2</sub>CO<sub>3</sub> (1.2 eq)/MeOH afforded elimination only, with trace amounts of starting material **102ea**

observed. The presence of elimination and cyclisation products were visible by TLC after only 5 mins at rt, suggesting both reactions were fast. Radical denitration of **497ca** was abandoned due to the low yields of ionic cyclisation.



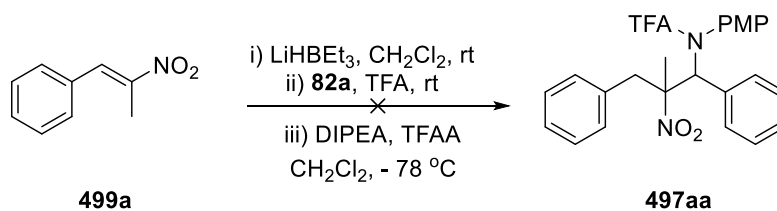
**Scheme 189.** Cyclisation to create a tertiary nitro centre, followed by protodenitration

The lack of success at alkylating the secondary  $\beta$ -nitroacetamides was unsurprising, and an alternative route was sought for the formation of a tertiary centre via the nitro-Mannich reaction. The formation of a tri-substituted nitroalkene for subjection to the reductive nitro-Mannich reaction was undertaken (**Table 29**), with nitromethane replaced by nitroethane for the formation of methyl-(*E*)-nitrostyrenes **499**. Initial attempts to form the vinyl nitrostyrene **499d** with nitroethane via general procedure B for aromatic aldehydes (Entry 1, **Table 29**) failed, giving a complex mixture. This is in contrast to the use of nitromethane under the same conditions, resulting in an 85 % yield of the di-substituted alkene **64d** (**Table 19**). Use of general procedure C proved more successful, affording intermediate **498d** in reasonable isolated yield (48 %). However  $^1\text{H}$  NMR analysis of the crude reaction had shown quantitative conversion before work up and purification, and material was lost to retro-addition during purification. In addition, the elimination step was very low yielding (10 %) using  $\text{MsCl}$ , DIPEA,  $0^\circ\text{C}$  (Entry 2). The reaction was therefore run a subsequent time without intermediate purification, in order to minimize retro-addition. The use of TFAA in place of  $\text{MsCl}$  and cooling the elimination step to  $-78^\circ\text{C}$  also led to an overall improved yield of 42 % over two steps (*c.f.* 5 %) (Entry 3). Under the same conditions, benzaldehyde **358a** afforded the corresponding tri-substituted nitrostyrene **499a** in a slightly higher yield (Entry 4).

**Table 29.** Formation of  $\alpha,\beta,\beta$ -trisubstituted nitrostyrenes

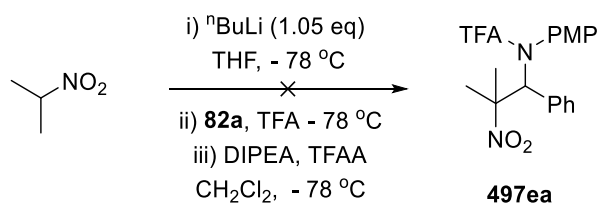
Entry	358	a	% Yield 498	b	% Yield 499
1	358d	NaOH/MeOH 0 °C	-	HCl, 0 °C	Complex mixture
2	358d	NEt <sub>3</sub> , rt	498d (48)	MsCl/DIPEA/ 0 °C	499d (10)
3	358d	NEt <sub>3</sub> , rt	-	TFAA/DIPEA/ - 78 °C	499d (42)
4	358a	NEt <sub>3</sub> , rt	-	TFAA/DIPEA/ - 78 °C	499a (47)

Nitrostyrene **499d** was subjected to the reductive nitro-Mannich reaction with imine **82a**/TFA at  $-78\text{ }^{\circ}\text{C}$ , however no product was observed. Nitrostyrene **499a** was then subjected to the reaction conditions, with imine **82a**/TFA added at room temperature (**Scheme 190**). Examination of the crude  $^1\text{H}$  NMR spectrum after nitro-Mannich reaction suggested the presence of the intermediate  $\beta$ -nitroamine with a *dr*  $\sim 70:30$ , however degradation occurred on TFA protection, and the desired  $\beta$ -nitroacetamide **497aa** was not isolated. TFA-protection of *N*-PMP  $\beta$ -nitroamines has been reported to be problematic in certain cases, for example the *syn,syn*-diastereoisomers formed from diethylzinc addition in conjugate-addition nitro-Mannich reaction,<sup>55</sup> and  $\beta$ -nitroamines formed from *t*-butyl or cyclohexyl-derived *N*-PMP imines.<sup>65</sup> It appears that the increased steric bulk around the nitro- or amino-centres render these  $\beta$ -nitroamines inert to TFA protection.



**Scheme 190.** Attempted formation of tertiary  $\beta$ -nitroacetamide **497aa**

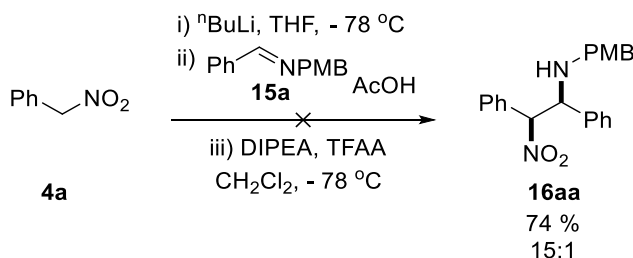
Tertiary  $\beta$ -nitroamine compounds have also been created by deprotonative nitro-Mannich reaction in this group from 2-nitropropane;<sup>5</sup> it was hoped deprotonation of similar secondary nitroalkanes would create a range of tertiary  $\beta$ -nitroacetamides. Unfortunately, degradation during *in situ* TFA protection of the crude  $\beta$ -nitroamine also took place, with no isolation of  $\beta$ -nitroacetamide **497ea** (**Scheme 191**). As previously suggested, this is likely due to steric congestion in the molecule; the formation of tertiary nitro centres via the nitro-Mannich reaction was thus abandoned, as TFA-protection is necessary to prevent decomposition of the  $\beta$ -nitroamines under the harsh conditions required for radical denitration.



**Scheme 191.** Attempted formation of tertiary  $\beta$ -nitroacetamide **497ea**

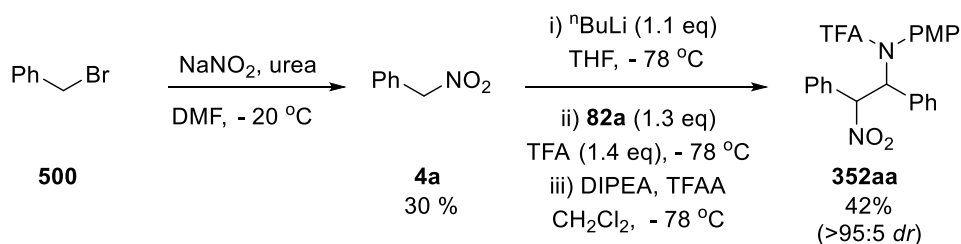
### 2.3.9.3 Formation of activated secondary $\beta$ -nitroacetamides

With the lack of success forming tertiary  $\beta$ -nitroacetamides, it was thought that activated secondary  $\beta$ -nitroacetamides may prove more accessible. The formation of  $\beta$ -nitroamine **16aa** from  $\alpha$ -nitrotoluene **4a** via the deprotonative nitro-Mannich reaction was known in the group. Interestingly, literature formation of **16aa** occurred with high diastereoselectivity for the *syn*-diastereoisomer (**Scheme 192**), in stark contrast to the usual *anti*-selectivity. In addition, the yield was reduced in comparison with other analogues, and attempted reduction of the nitro group using a mild  $\text{SmI}_2$  procedure had resulted in decomposition due to the instability of the  $\beta$ -nitroamine.<sup>5</sup>



**Scheme 192.** Previous synthesis of an activated secondary β-nitroamine by the Anderson group

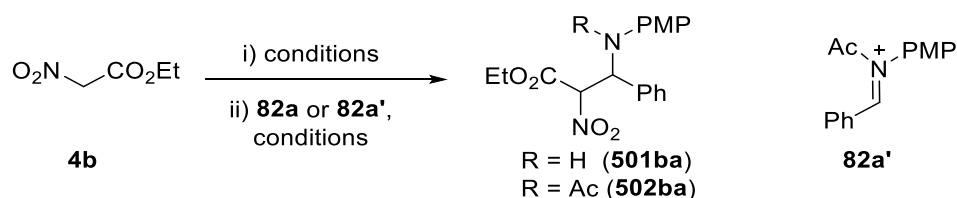
It was thought that subjection of α-nitrotoluene **4a** under similar conditions, with substitution of the *N*-PMB imine **15a** for the *N*-PMP imine **82a** and a switch from AcOH to TFA should be possible. The expense of α-nitrotoluene necessitated its production on scale from benzyl bromide. It was found that the use of sodium nitrite/urea in DMF proved successful on a large scale for the conversion of benzyl bromide to α-nitrotoluene in 30 % yield (lit. 55 %).<sup>256</sup> The nitro-Mannich reaction of α-nitrotoluene **4a** with imine **82a** afforded crude β-nitroacetamide **352aa** as a mixture of diastereoisomers (70:30), however upon recrystallisation this could be reduced to a single isomer in 42 % yield. The single isomer was not definitively characterised as *syn*- or *anti*-, however the configuration is unimportant due to the racemisation of the nitro centre on the formation of a planar carbon radical. The moderate yield may be explained by the instability of the molecule due to steric congestion between the two phenyl groups, as the equivalent *N*-PMB protected β-nitroamine was observed to be particularly unstable.<sup>5</sup>



**Scheme 193.** Formation of secondary activated β-nitroacetamide **352aa**

A higher degree of stability is afforded to carbon radicals by electron withdrawing groups such as nitriles and esters.<sup>146</sup> The formation of a carbonyl-stabilised β-nitroacetamide was attempted by the use of ethyl nitroacetate **4b** as a nucleophile for the nitro-Mannich reaction. Unfortunately, under a range of conditions attempted, no β-nitroamines **501ba** or β-nitroacetamides **502ba** were obtained (**Scheme 194**). Deprotonation with <sup>n</sup>BuLi followed by trapping with imine **82a**/TFA was unsuccessful at -78 °C and on warming to rt; stirring ethyl nitroacetate **4b** with imine **82a'** at rt for 1 d also proved unsuccessful.

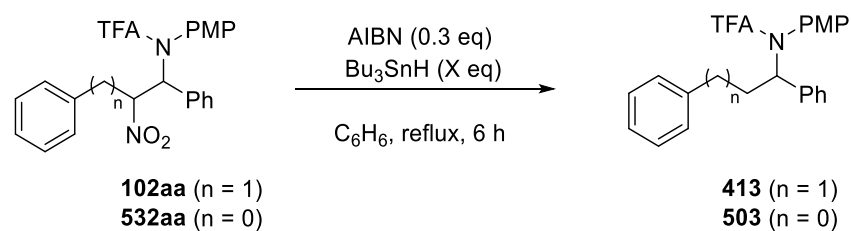
Use of  $\text{NEt}_3$  with both imines **82a** and **82a'** at rt also proved unsuccessful, with formation of a complex mixture. Deprotonation with  $^n\text{BuLi}$  followed by reaction with **82a'** at  $-78\text{ }^\circ\text{C}$  proved slightly more promising, however it was decided to focus on radical denitration of the  $\alpha$ -nitrotoluene derived  $\beta$ -nitroacetamide **352aa**.



**Scheme 194.** Attempted formation of ester-stabilised  $\beta$ -nitroamine **501ba** or  $\beta$ -nitroacetamide **502ba**

### 2.3.10 Radical denitration of an activated 2° $\beta$ -nitroacetamide

With activated secondary  $\beta$ -nitroacetamide **352aa** in hand, the yield of protodenitration product **503** was investigated under the same conditions previously used, with variation in the concentration of TBTH. The equivalents of TBTH used for the reaction were analogous to those investigated for the protodenitration of **102aa**; a comparison is shown in **Table 30**. The difference in yield from the activation of the nitro position is evident at 2 eq TBTH, with a yield of only 4 % in either benzene or toluene of **413** (Entry 2, **Table 30**) compared to a yield of 10 % in benzene or 42 % in toluene of **503** (Entry 2). A good yield of 55 % **503** is achieved with 5 eq TBTH (*c.f.* 17 % **413**, Entry 3); at 10 eq TBTH, a very good yield is obtained for both **413** and **503** (~ 70 – 80 %, Entry 4).

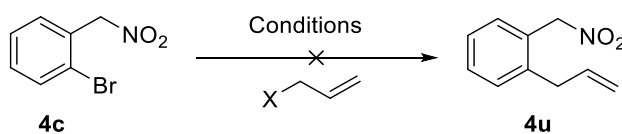
**Table 30.** Protodenitration of **352aa** and comparison with unactivated **102aa**

Entry	X	% Yield <sup>a</sup> <b>413</b>	% Yield <sup>b</sup> <b>503</b>
<b>1</b>	1.2	< 1	1
<b>2</b>	2	4 (4) <sup>b</sup>	10 (42) <sup>a</sup>
<b>3</b>	5	17	55
<b>4</b>	10	79 <sup>2</sup>	71

<sup>a</sup>Run in PhCH<sub>3</sub> <sup>b</sup>Run in C<sub>6</sub>H<sub>6</sub>

### 2.3.11 Formation of tethered activated 2° radical precursors

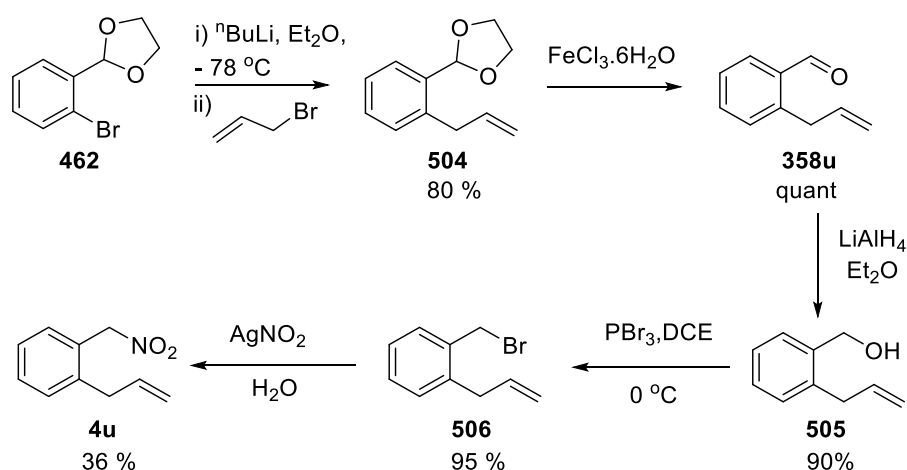
The generation of a range of activated secondary radical cyclisation precursors similar to those already created was first attempted by the generation of an allyl benzene tether; the placement of the benzene ring would afford activation of the nitro group (**Table 31**). It was thought this could be formed from allylation of 2-bromo- $\alpha$ -nitrotoluene **4c** to give 2-allyl- $\alpha$ -nitrotoluene **4u**, which could be subjected to the nitro-Mannich reaction. Nitration of 2-bromobenzylbromide with AgNO<sub>2</sub> afforded 2-bromo- $\alpha$ -nitrotoluene **4c** in 39 % yield.<sup>257</sup> Allylation of **4c** via a range of methodologies was attempted. Stille coupling<sup>258</sup> of **4c** with allyl tributyltin (Entry 1, **Table 31**) gave no product **4u**, degradation of starting material was observed. Formation of an aryl Grignard reagent followed by an iron (III) catalysed coupling reaction with allyl acetate gave recovered **4c** (Entry 2).<sup>259</sup> Attempted radical allylation also proved unsuccessful (Entry 3), as did Grignard exchange followed by copper (I) catalysed addition to allyl bromide (Entry 4).<sup>260</sup>

**Table 31.** Attempted allylation of 2-bromo- $\alpha$ -nitrotoluene

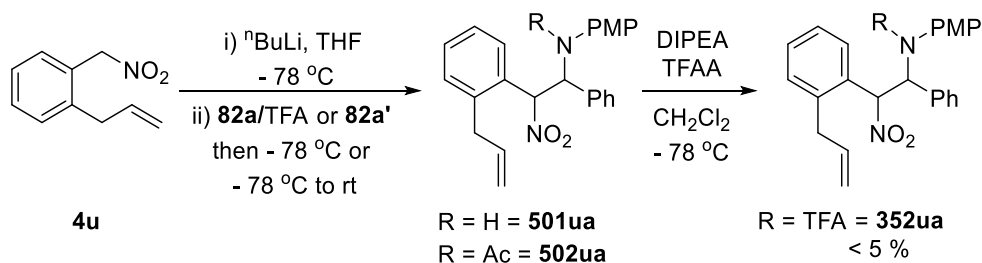
Entry	Reagents/Conditions	X	Result
1	Pd(PPh <sub>3</sub> ) <sub>4</sub> (5 mol %), DMF Sealed tube/110 °C/1 d	SnBu <sub>3</sub>	degradation
2	i) Mg, LiCl, THF/18 h ii) Fe(acac) <sub>3</sub> , THF/0 °C/5h	OAc	No reaction
3	AIBN, Toluene/reflux/8 h	SnBu <sub>3</sub>	No reaction
4	i) <sup>i</sup> PrMgCl.LiCl, THF/– 15 °C ii) CuI/THF – 10 °C	Br	No reaction

Perhaps unsurprisingly, 2-allyl- $\alpha$ -nitrotoluene **4u** is a novel compound, which may suggest it is difficult to make via direct methods. However it was noted that the equivalent bromide **506** could be prepared via a long but high yielding synthetic route (**Scheme 195**); it was thought that the nitration of bromide **506** using silver nitrite<sup>257</sup> should provide a route to the nitroalkane. Initial attempted Grignard formation from **462** followed by addition to allyl bromide proved unsuccessful, however, allylation via halogen-lithium exchange<sup>261</sup> was found to be successful, affording **504** in very good yield. De-acetalisation using FeCl<sub>3</sub>.6H<sub>2</sub>O<sup>262</sup> gave essentially quantitative yield of aldehyde **358u**, which was itself reduced to the corresponding alcohol by LiAlH<sub>4</sub> in excellent yield; bromination of the alcohol with PBr<sub>3</sub> afforded the desired bromide **506** also in excellent yield (**Scheme 195**).<sup>243</sup> Nitration of the bromide using AgNO<sub>2</sub> afforded 2-allyl- $\alpha$ -nitrotoluene **4u** in 36 % yield, a variety of alternative reaction pathways exist under these conditions, accounting for the moderate yield.<sup>256</sup>

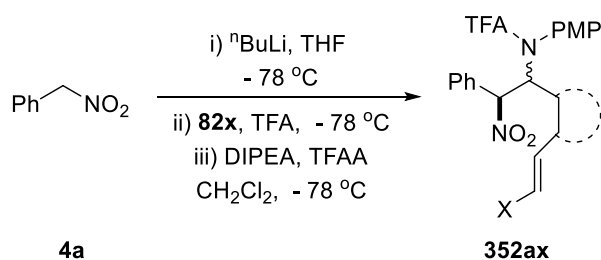


Scheme 195. Synthesis of 2-allyl- $\alpha$ -nitrotoluene **4u**

With 2-allyl- $\alpha$ -nitrotoluene **4u** in hand, it was subjected to the nitro-Mannich reaction. Deprotonation using  $n\text{BuLi}$ , followed by reaction with imine **82a**/TFA and the usual protection step (TFAA/DIPEA) afforded only a trace amount of the desired  $\beta$ -nitroacetamide **352ua**. Examination of conversion to the intermediate  $\beta$ -nitroamine **501ua** by  $^1\text{H}$  NMR indicated a conversion of 44 % on addition of imine **82a**/TFA and stirring at  $-78\text{ }^\circ\text{C}$  for 1 h followed by stirring at rt for 1 h. It would appear that TFA protection of the crude  $\beta$ -nitroamine **501ua** was problematic, with only trace amounts of **352ua** observed. This was unexpected due to the successful TFA-protection affording the non-allyl tethered analogue **352aa** and suggests that the extra steric bulk afforded by the allyl group makes TFA protection difficult. Attempted nitro-Mannich reaction of **4u** via deprotonation with  $n\text{BuLi}$  followed by the addition of acetylated imine **82a'** resulted in mainly recovery of **4u** and degradation of imine **82a'**, with traces of possible product. However with such low yields and a 5-step synthesis for the generation of the starting nitro compound **4u**, the route seemed implausible, and was abandoned.

Scheme 196. Attempted formation of tethered activated secondary  $\beta$ -nitroacetamides

The formation of activated secondary  $\beta$ -nitroacetamides with alkene tethers was thus investigated with the addition of  $\alpha$ -nitrotoluene **4a** to a range of alkenyl tether-containing imines previously generated in this work (**Table 32**).



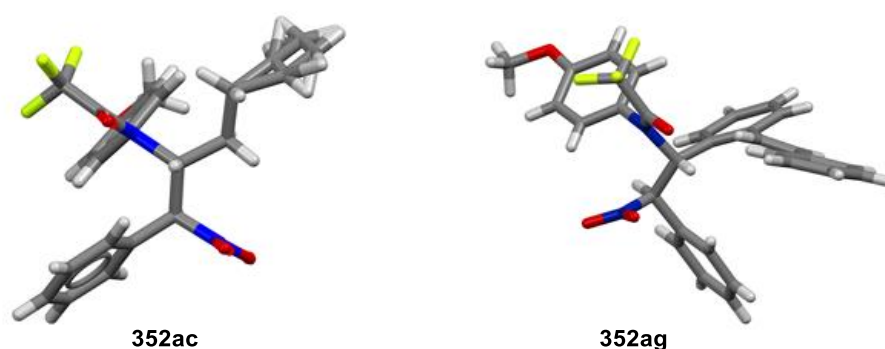
**Table 32.** Formation of activated secondary  $\beta$ -nitroacetamides **352ax** for radical cyclisation

Entry	Imine	$\beta$ -nitroacetamide
1	<p style="text-align: center;"><b>82c</b></p>	<p style="text-align: center;"><b>352ac</b></p> <p style="text-align: center;">55 % (&gt;95:5 <i>dr</i>)</p>
2	<p style="text-align: center;"><b>82d</b></p>	<p style="text-align: center;"><b>352ad</b></p> <p style="text-align: center;">(No product observed)</p>
3	<p style="text-align: center;"><b>82g</b></p>	<p style="text-align: center;"><b>352ag</b></p> <p style="text-align: center;">11 % (&gt; 95:5 <i>dr</i>)<sup>a</sup></p>

<sup>a</sup>After recrystallisation

Nitro-Mannich reaction of **4a** with imine **82c** successfully afforded  $\beta$ -nitroacetamide **352ac** after TFA protection, in good yield and excellent diastereoselectivity (Entry 1,

**Table 32**). The  $^1\text{H}$  NMR spectrum of **352ac** was very broad; better resolution was achieved on heating to 60 °C, with full characterisation as far as possible. A crystal structure of **352ac** confirmed the correct structure, and also the stereochemistry as the expected *anti*-orientation (**Fig. 27**). In contrast, trapping of the nitronate generated from **4a** with styryl-tethered imine **82d** resulted in the formation of a complex mixture (Entry 2). No product **352ad** could be obtained from the product mixture. The nitro-Mannich reaction of **4a** with stilbene imine **82g** followed by TFA protection resulted in the isolation of  $\beta$ -nitroacetamide **352ag** in low yield (Entry 3). The crude product was a complex mixture by  $^1\text{H}$  NMR hence diastereoselectivity of the product could not be ascertained precisely, however **352ag** appeared by  $^1\text{H}$  NMR to be the major diastereoisomer. Purification of the crude by both column chromatography and recrystallisation afforded pure **352ag** as a single diastereoisomer; it was definitively assigned as the *syn*-diastereoisomer by crystal structure (**Fig. 27**). The low yield of **352ag** was attributed to the instability of the product<sup>5</sup> due to the close proximity of the two phenyl rings; in this case the stilbene tether provided extra steric bulk, which would be expected to further destabilise the product. Interestingly, an 11 % yield of this product **352ag** was formed, whereas the styryl tethered product **352ad** was not observed (Entry 3 vs Entry 2). This could be due to side-reactions of the styryl tether. The second phenyl ring on the styrene moiety of tethered imine **82g** could have provided a shielding effect on the alkene; in addition, the more conjugated alkene would be less nucleophilic, leading to a reduction in the formation of by-products.

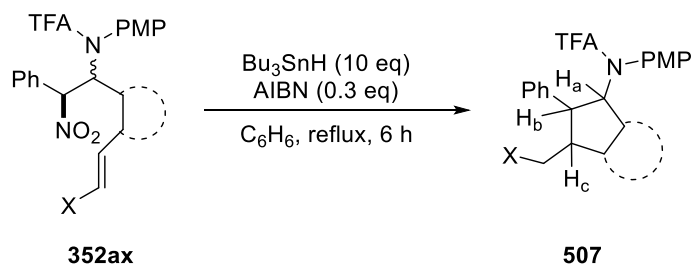


**Fig. 27.** Crystal structures confirming the structure and relative stereochemistry of **352ac** and **352ag**

### 2.3.12 Radical cyclisation of tethered activated 2° radical precursors

With activated secondary  $\beta$ -nitroacetamides **352ac** and **352ag** in hand, subsection to radical conditions previously described was attempted. It should be mentioned that a

reduction in the equivalents of TBTH from 10 to 5 would most probably have given reasonable yields, as activated secondary nitro groups are known to be more conducive to radical denitration, and a lower TBTH loading has been used.<sup>145-146</sup> However for continuity and in addition to investigate whether protodenitration or cyclisation would be the preferred route at this high loading, 10 eq TBTH was used. Due to lack of time, unfortunately it was not possible to run additional denitration-cyclisation reactions with a lower TBTH loading.



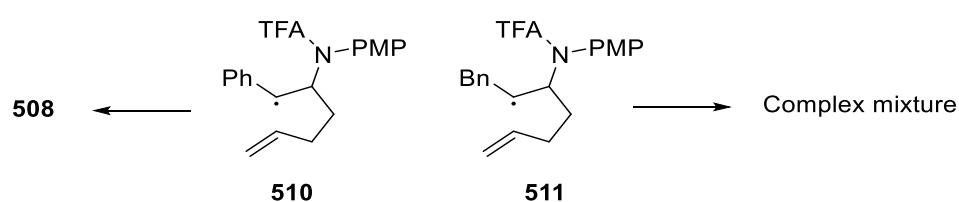
**Table 33.** Radical denitration-cyclisation of activated secondary  $\beta$ -nitroacetamides **352ax**

Entry	$\beta$ -nitroacetamide	Product
1	<p><b>352ac</b></p>	<p><b>508</b> 41 %<sup>a</sup> (&lt; 36 %, 50:50 <i>dr</i>)</p>
3	<p><b>352ag</b></p>	<p><b>509</b> 13 % (95:5 <i>dr</i>)</p>

<sup>a</sup>Conversion by mass and  $^1\text{H}$  NMR

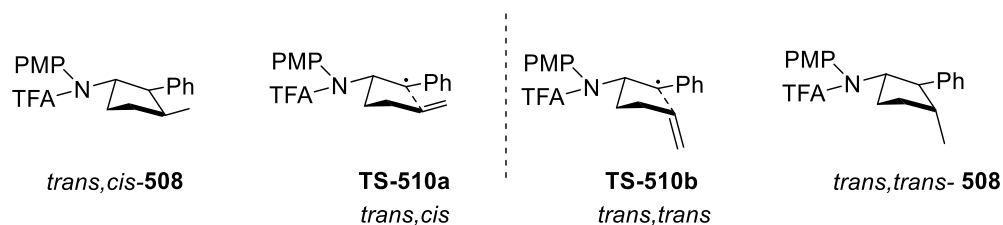
Subjection of  $\beta$ -nitroacetamide **352ac** to the general radical denitration conditions described (Entry 1, **Table 33**) resulted in the formation of a mixture of products. The expected cyclopentane **508** was isolated in moderate yield, as an inseparable 50:50 mixture of diastereoisomers, and with a trace of unknown product (hence < 36 %). This

unknown product was hypothesised to be a product of decomposition of the starting  $\beta$ -nitroacetamide **352ac** via elimination, and did not contain the PMP protecting group, however no nitroalkene peak was observed; the presence of TFA-NH-PMP **364** also confirmed that some elimination had taken place. The sterically more hindered activated secondary  $\beta$ -nitroacetamides **352** are likely to be more prone to elimination due to the release of steric strain on loss of **364** as a leaving group. Activation of the secondary nitro group by the adjacent benzene ring resulted in successful cyclisation of the activated secondary radical **510**. This is in contrast to the unactivated secondary radical **511** (**102ac**) which afforded a complex mixture (**Scheme 197** and **Tables 16 & 33**).



**Scheme 197.** Secondary vs activated secondary cyclisation of an acetamide-substituted tether

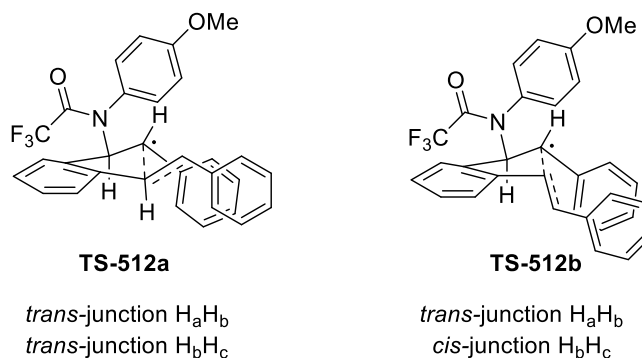
The *dr* (50:50) for radical cyclisation of **352ac** is similar to that observed for unactivated secondary  $\beta$ -nitroacetamides **102ax** which contain a 2-acetamido-substituted styryl tether (**Scheme 153**, **Table 25**), which afforded tentatively assigned *trans,trans*- and *trans,cis*- diastereoisomers in preference. It was likely that in this case, a 50:50 ratio of the *trans,trans*- and *trans,cis*- diastereoisomers was also obtained, however due to the complex nature of the  $^1\text{H}$  NMR, this could not be ascertained. The formation of *trans,trans*- and *trans,cis*-tri-substituted cyclopentane rings from 1,2-substituted hexenyl radicals is known,<sup>172</sup> due to the placement of the majority of substituents in *pseudo*-equatorial positions in a chair- or boat like transition state (**Fig. 28**).



**Fig. 28.** Theoretically more favourable transition states for radical cyclisation of **352ac**

Radical cyclisation of the stilbene-tethered  $\beta$ -nitroacetamide **352ag** afforded the expected indane product **509** in a much lower yield (Entry 2). It is unsurprising that radical cyclisation of such a sterically bulky radical tether resulted in a lower yield than the

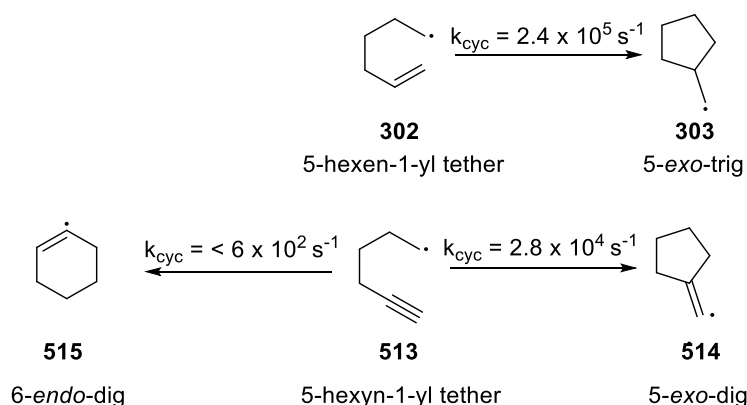
equivalent unactivated secondary  $\beta$ -nitroacetamide **102ag**, which underwent cyclisation in 34 % yield (*c.f.* 13 %). It would appear that the extra steric bulk at the radical centre also leads to an increase in diastereoselectivity (60:40 to 95:5 *dr*). Traces of the minor isomer in the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra mean that characterisation of the major isomer was possible. Analysis of the NOESY interactions between protons  $\text{H}_a\text{-H}_b$  (w),  $\text{H}_b\text{-H}_c$  (w) and  $\text{H}_a\text{-H}_c$  (m) and the  $^3J_{\text{H}_a\text{H}_b}$  and  $^3J_{\text{H}_b\text{H}_c}$  values (9.4 &  $\sim 9.0$  Hz respectively) of **509** led to the tentative assignment of the major diastereoisomer as the *trans,trans*-configuration. The loss of a  $\text{CH}_2$ -unit  $\alpha$ -to the radical centre (**Fig. 29**) gives more steric crowding in the transition states **TS-512a** and **TS-512b**. It was likely that this rendered the *trans,trans*-placement (**TS-512a**) of all substituents in *pseudo*-equatorial positions lower in energy, due to fewer destabilising steric interactions, leading to a greater population of this transition state and a resulting enrichment of the *dr*.



**Fig. 29.** Increase in steric crowding in the transition states for activated secondary  $\beta$ -nitroacetamide **352ag**

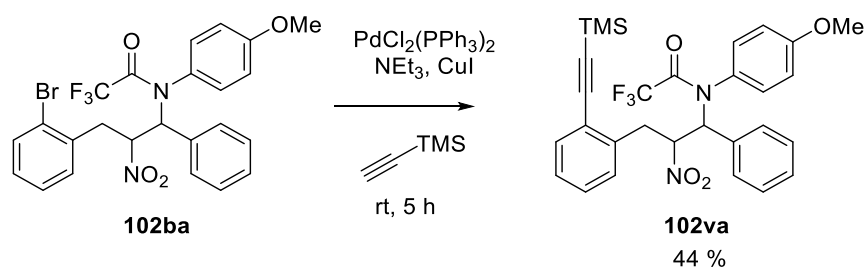
### 2.3.13 Formation of radical precursors containing an alkyne tether

With successful radical denitration and 5-*exo*-trig cyclisation of  $\beta$ -nitroacetamides on to  $\text{sp}^2$  carbons, expansion to 5-*exo*-dig cyclisation on to  $\text{sp}$ -hybridised carbon centres was attempted, with the installation of 5-hexyn-1-yl-type tethers. The addition of radicals to alkynes is a useful process due to the formation of highly reactive vinyl radicals *in situ*, which are then able to undergo further carbon-carbon bond formation or hydrogen abstraction, leaving an alkene as a new synthetic handle. The 5-hexyn-1-yl radical cyclisation is slower than the 5-hexen-1-yl cyclisation ( $k_{\text{cyc}} = 2.8 \times 10^4 \text{ s}^{-1}$  (5-*exo*-dig) *c.f.*  $k_{\text{cyc}} 2.4 \times 10^5 \text{ s}^{-1}$  (5-*exo*-trig)), with 5-*exo*-dig cyclisation still highly preferred<sup>263</sup> compared to the 6-*endo*-dig alternative ( $k_{\text{cyc}} = < 6 \times 10^2 \text{ s}^{-1}$ ).<sup>214b, 264</sup>



**Scheme 198.** Cyclisation rates of 5-hexen-1-yl vs 5-hexyn-1-yl radicals

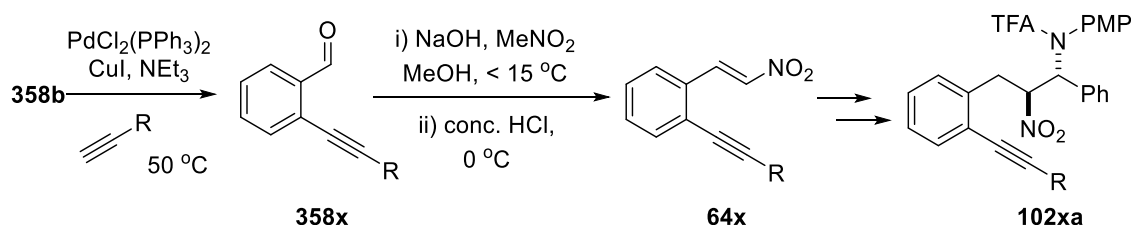
With  $\beta$ -nitroacetamide **102ba** already in hand, initial attempts at the addition of an alkyne chain to the molecule via the Sonogashira coupling of TMS acetylene with **102ba** was attempted (**Scheme 199**). Although successful in a moderate yield, the product **102va** could not be separated from residual starting material **102ba**. In addition, a subsequent reaction run on larger scale was unsuccessful.



**Scheme 199.** Attempted Sonogashira coupling of **102ba** with alkynyl-TMS

The formation of an alkynyl tether prior to the nitro-Mannich reaction was then attempted. Coupling of TMS acetylene with 2-bromobenzaldehyde **358b** afforded **358v** in excellent yield. Subjection of 2-alkynylaldehyde **358v** to the Henry reaction using NaOH/MeNO<sub>2</sub>/MeOH followed by *in situ* elimination using HCl (general procedure B)<sup>65</sup> resulted in the isolation of nitroalkene **64v** in 62 % yield. Use of NEt<sub>3</sub>/MeNO<sub>2</sub> followed by MsCl/DIPEA *in situ* elimination (General procedure C)<sup>65</sup> resulted in a lower yield of 50 %. Reductive nitro-Mannich reaction of **64v** with imine **82a** afforded  $\beta$ -nitroacetamide **102va** in good yield and excellent *dr*, with the major isomer assigned as the *anti*-diastereoisomer based on group precedent (Entry 1, **Table 34**).<sup>62</sup> The same synthetic scheme was applied for the synthesis of the alkynyl tether where R = Ph; aldehyde **358w** was obtained in excellent yield and subjected to Henry reaction using the NaOH/MeNO<sub>2</sub>/MeOH method, followed by elimination to afford nitroalkene **64w** in very

good yield. Subjection of **64w** to the reductive nitro-Mannich reaction and TFA protection afforded  $\beta$ -nitroacetamide **102wa** in good yield however with lower diastereoselectivity (Entry 2, **Table 34**). Recrystallisation of **102wa** (90:10 *dr*) from Et<sub>2</sub>O/hexanes gave a single diastereoisomer **102wa** (38 %).



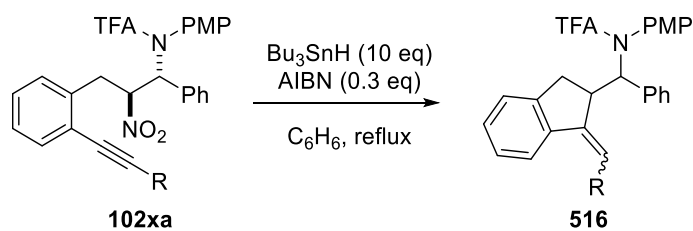
**Table 34.** Preparation of 2-alkynylphenyl  $\beta$ -nitroacetamides **102xa**

Entry	R ( <b>102xa</b> )	% Yield <b>358</b>	% Yield <b>64</b>	% Yield <b>102</b>
1	TMS ( <b>102va</b> )	88	62	58 (> 95:5 <i>dr</i> )
2	Ph ( <b>102wa</b> )	93	75	65 (90:10 <i>dr</i> )

### 2.3.14 Radical cyclisation of alkynyl-tethered radical precursors

With silyl- and phenyl-alkynyl derivatives **102xa** in hand, radical cyclisation under the general conditions (10 eq TBTH, 0.3 eq AIBN, C<sub>6</sub>H<sub>6</sub>, reflux) was attempted (**Table 35**). Cyclisation of TMS-alkynyl tether **102va** was successful, affording two main products, **517** and **518** in low yields (moderate conversion). It was hypothesised that 5-*exo*-dig cyclisation had afforded two types of *exo*-methylene indanes, via hydrogen abstraction of the intermediate radical (**517**), or 1,4-phenyl migration reaction followed by hydrogen abstraction (**518**). Recrystallisation of a mixture of both products afforded pure **518**. Assignment of the structure of **518** was based on MS and NMR analysis. Confirmation of the expected molecular peak at 510.2070 (*M* + *H*<sup>+</sup>) suggested that an isomer of the expected product **517** was present, however a peak at 291 (6%) resulting from cleavage of the C-CN bond was observed, implying that the phenyl ring was present on the left-hand structure of the molecule (**518**). The presence of CH<sub>2</sub>N peaks at  $\delta$  2.90 ppm (1H, dd, *J* = 13.3, 3.3 Hz) and 4.01 ppm (1H, dd, *J* = 13.1, 11.5 Hz) corresponding to a CH<sub>2</sub>N peak at  $\delta$  52.3 ppm also suggested that fragmentation had occurred, due to the similar <sup>1</sup>H and <sup>13</sup>C NMR peaks found in previous 1,4-phenyl translocation products **421**, **491** and **493**.

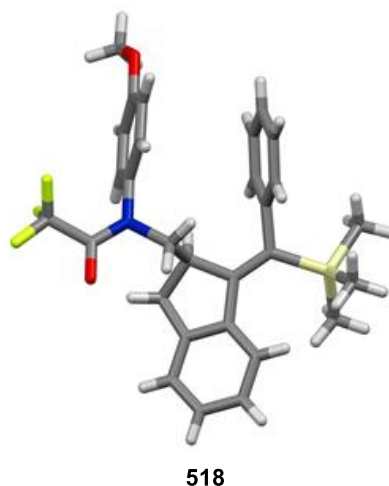


**Table 35.** Radical cyclisation of 2-alkynylphenyl β-nitroacetamides **102xa**

Entry	R (102)	% Yield <b>516</b> <sup>a</sup>
1	TMS ( <b>102va</b> )	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p><b>517</b></p> <p>&lt; 15<sup>c</sup> (21)<sup>b</sup></p> </div> <div style="text-align: center;"> <p><b>518</b></p> <p>6 (30)<sup>b</sup></p> </div> </div>
2	Ph ( <b>102wa</b> )	<div style="text-align: center;"> <p>Complex mixture</p> <p><b>519</b></p> <p>(&lt; 10 %)<sup>ad</sup></p> </div>

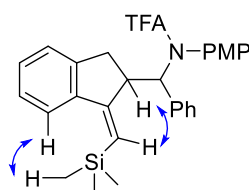
<sup>a</sup>Isolated yield <sup>b</sup>Conversion <sup>c</sup>Contains impurities - < 20 % <sup>d</sup>Contains impurity - ~15 %

A correlation table for the assignment of **518** can be found in the appendices, proton and carbon NMR was assigned based on the use of HSQC and HMBC spectra. A crystal structure of the fragmentation product **518** was obtained, which confirmed the assigned structure (**Fig. 30**). The definitive assignment of **518** as a product of 1,4-phenyl radical migration by X-ray crystallography further corroborates the assignment of **421**, **491** and **493**.



**Fig. 30.** X-Ray crystal structure of **518**, showing the 1,4-phenyl translocation

Indane **517** could not be isolated pure (~ 15 - 20 % impurity), however it was assigned as far as possible. Analysis by LRMS (EI) gave a fragmentation pattern in agreement with **517**, cleavage about the C-CN bond gave rise to fragments at 308 (100 %,  $\text{C}_{16}\text{H}_{13}\text{F}_3\text{NO}_2^+$ ) and 202 (37 %,  $\text{C}_{13}\text{H}_{18}\text{Si}^+$ ), only trace amounts of the molecular ion peak at 509 (< 5 %,  $\text{M}^+$ ) were observed. Analysis of the  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra confirmed the presence of a *CH* alkene peak at  $\delta$  5.99 ppm (1H, s), expected for an *exo*-methylene indane **517**. Analysis by COSY, HMQC and HMBC supported the structure **517** suggested (see appendices for correlation table). The geometry of the alkene was confirmed by NOE interactions observed between the  $\text{Si}(\text{CH}_3)_3$  protons and the adjacent aromatic *ortho*-proton on the indane ring, and also between the *CHSi* proton and the *CHCHN* proton, indicating the alkenyl *CHSi* proton faces away from the indane ring (**Fig. 31**).

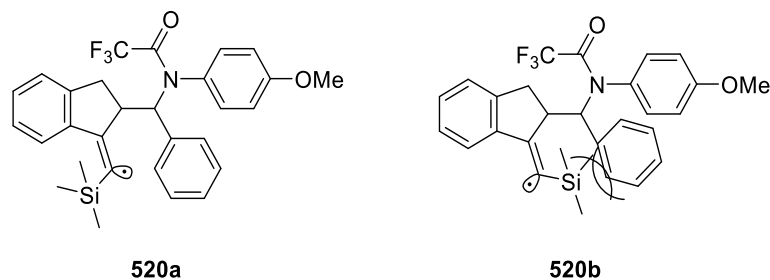


**Fig. 31.** NOE analysis of the alkene geometry showing through-space interactions

Radical cyclisation of  $\beta$ -nitroacetamide **102wa** was more problematic; analysis of the crude  $^1\text{H}$  NMR gave a complex mixture of products, including approximately 50 % starting material. Attempted purification resulted in the isolation of a mixture of products, unfortunately recrystallisation did not result in separation of the compounds. It appeared that the main product in this mixture was a phenyl analogue of **517**, MS analysis gave the molecular ion peak at 514 ( $\text{M} + \text{H}^+$ ), with a fragment ion at 295 (33 %,  $\text{C}_{23}\text{H}_{19}^+$ )

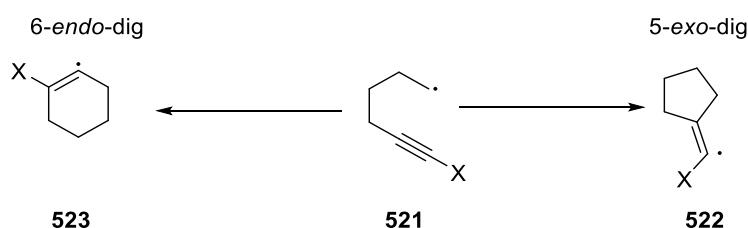
corresponding to a loss of TFA-NH-PMP from **519**. A peak at 615 (24 %) may be attributed to an impurity, however this could not be identified. Analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **519** show a  $\text{CHN}$  peak at  $\delta$  6.23 – 6.27 ppm (2H, m) which overlaps with an alkene  $\text{CH}$  peak; HSQC shows correspondence between these peaks and those at  $\delta$  64.4 and 124.4 ppm ( $\text{CHN}$  and alkene  $\text{CH}$  respectively). Much of the rest of the molecule could not be assigned as it was mainly aromatic signals, however characterisation was carried out as far as possible. Orientation of the alkene could not be ascertained due to the complex mixture of aromatic peaks and the overlap of the  $\text{CHN}$  and alkene  $\text{CH}$  peaks.

It appeared that radical cyclisation of both  $\beta$ -nitroacetamides **102va** and **102wa** resulted in the formation of complex mixtures, in which only the major products **517** and **518**, and **519** could be isolated. In both cases, cyclisation occurred with the formation of tri-substituted alkenyl indanes **516** in roughly similar isolated yields (< 15 % **517**, < 10 % **519**), with the isolation of tetra-substituted alkene **518** where  $\text{R} = \text{SiMe}_3$ . The stability of vinyl radicals **520** is lower than that of alkyl radicals, due to the lack of stabilisation of the SOMO by hyperconjugation.<sup>238</sup> Subsequent reactions of vinyl radicals are therefore very fast, and it is not unexpected that 1,4-phenyl translocation has occurred in higher yield for alkyne **102va** (30 % conversion) than observed for the products of radical cyclisation on to alkenes **421**, **491** and **493**. The lack of 1,4-phenyl translocation of the phenyl derivative may in part be due to the inability to isolate any of this product, however it was also possible that 1,4-phenyl translocation is unfavourable to the formation of a sterically bulky tetra-substituted alkene. Interestingly, only one isomer of the hydrogen-abstraction product **516** is observed, the (*Z*)-alkene. Interconversion of vinyl radicals occurs, leading to mixtures of alkene geometric isomers,<sup>238</sup> however in this case the steric bulk of the phenyl and trifluoroacetamide may have rendered the (*E*)-orientation of the intermediate TMS-vinyl radical unfavourable (**Fig. 32**).



**Fig. 32.** Proposed unfavourable steric interactions between the TMS and phenyl/TFANHPMP substituents in an (*E*)-alkene

No isolation of any 6-*endo*-dig product 6-membered rings (tetralyl isomers) was observed. This was expected due to the more favourable orbital overlap of the SOMO with the  $\pi^*$  LUMO of the alkyne; although 6-*endo*-dig cyclisation is possible it is unfavourable and the activation energy for 5-*exo*-dig cyclisation is much lower. Substitution of the alkyne by Ph/TMS can further lower the activation energy needed for 5-*exo*-trig cyclisation significantly in comparison to the equivalent 6-*endo*-dig cyclisation; whilst the 5-hexyn-1-yl tether does not take into account the planarity of the styrynyl- system, it provides a general guideline for the effect of the Ph and TMS substituents on the alkyne (**Table 36**). It would appear that 5-*exo*-dig cyclisation of the 5-hexyn-1-yl tether is favoured by substitution at C-6 by Me/Ph/TMS compared to the parent alkyne **521** (X = H). The effect is greatest where X = Ph, resulting in a large reduction in  $E_a$  of 2.84 kcal mol<sup>-1</sup>, the effect is less pronounced for substitution by TMS, resulting in a reduction in  $E_a$  of only 0.36 kcal mol<sup>-1</sup> (Entries 3 & 4, **Table 36**). In practise, the yield for the styrynyl TMS derivative **102va** was higher than that of the phenyl derivative **102wa**, it is unclear why this occurred however this may be partly due to increased steric bulk in the planar radical transition state.



**Table 36.** Calculated activation energies of 5-*exo*- vs 6-*endo*-dig cyclisation<sup>263b</sup> of **521**

Entry	521 (X = )	$E_a/\text{kcal mol}^{-1}$ (522)	$E_a/\text{kcal mol}^{-1}$ (523)
1	H	7.29	9.91
2	Me	7.10	10.35
3	Ph	4.45	11.88
4	SiMe <sub>3</sub>	6.74	12.00

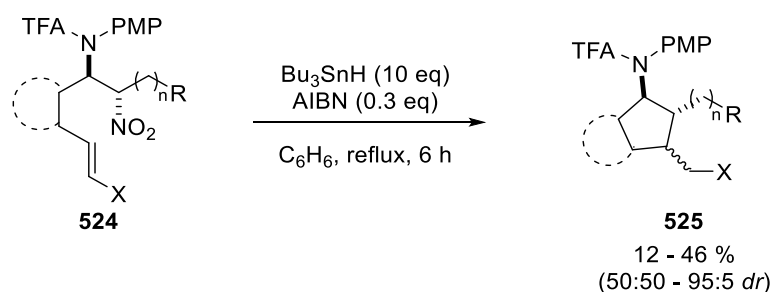
Indanes **516** were isolated as single diastereoisomers **517** and **519** of unknown relative stereochemistry, it was not possible to rule out the formation of the alternative diastereoisomer of the phenyl-derivatives **519** due to the complex nature of the crude <sup>1</sup>H

NMR. The crude  $^1\text{H}$  NMR from cyclisation of the TMS derivative showed the presence of a possible minor diastereoisomer, however a *dr* could not be obtained due to the complex  $^1\text{H}$  NMR spectrum. It was hypothesised that this enrichment in diastereoselectivity was caused by an increase in energy of one of the diastereomeric transition states due to increased rigidity of the alkynyl tether *c.f.* the alkenyl tether. No direct comparison between the yields expected for the TMS-substituted derivative **102va** and an alkenyl equivalent can be made. However radical cyclisation of the phenyl-substituted styryl derivative **102ga** resulted in the isolation of a higher yield of indane **471** (47 %) than that achieved for radical cyclisation of phenyl-substituted alkynyl derivative **102ga**, yielding indane **519** in < 10 % yield (21 % conversion). This was expected due to the slower rate of intramolecular addition of radicals to alkynes vs alkenes (Scheme 198).

### 2.3.15 Intramolecular cyclisations: conclusions and future work

#### 2.3.15.1 Conclusions

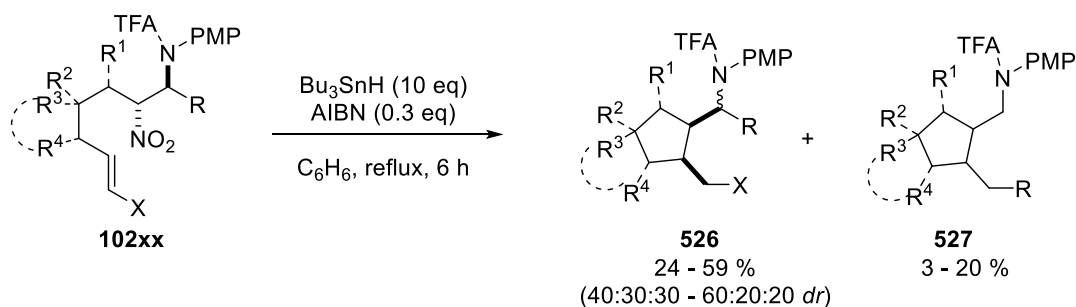
This chapter described the synthesis of a range of  $\beta$ -nitroacetamides, containing a variety of alkenyl- or alkynyl tethered precursors for radical cyclisation, and the subjection of these precursors to the radical denitration-cyclisation conditions developed. It was found that intramolecular cyclisation could be performed on a variety of secondary and activated secondary  $\beta$ -nitroacetamides at lower temperature (refluxing in benzene *c.f.* toluene) by increasing the equivalents of TBTH used (to 10) and increasing substitution of the tether. The formation of 2-acetamido indanes or cyclopropanes **525** was achieved in 12 – 46 % yield with 50:50 to 95:5 % *dr*, tentatively assigned as the *trans,trans*- and *trans,cis*-isomers where assignment could be made (Scheme 200).



**Scheme 200.** Radical cyclisation of 2-aminotethered  $\beta$ -nitroacetamides **524**

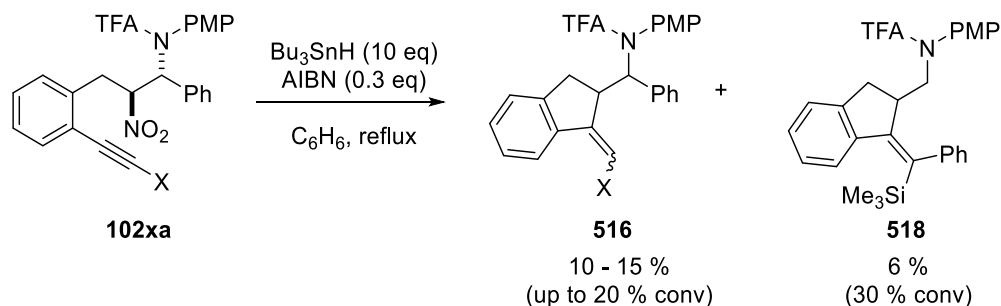
Cyclisation of  $\beta$ -nitroacetamide precursors **102xx** led to the formation of substituted indanes or cyclopentanes **526** in yields of 24 – 59 % with 40:30:30 – 60:20:20 *dr*. The

formation of fragmentation products **527** only occurred where X = H and these products were obtained in 3 – 20 % yield, as one diastereoisomer (**Scheme 201**). Tentative assignment of indanes **526** relative to a crystal structure obtained (*vide infra*) gave a major *cis*-orientation across the ring (~ 80 %) with and approximately equal ratio *cis,cis*- and *cis,trans* relative stereochemistry. The relative stereochemistry of the fragmentation isomers was not clear in all cases, however some are tentatively assigned as *cis*.



**Scheme 201.** Radical cyclisation of substituted  $\beta$ -nitroacetamides **102xx**

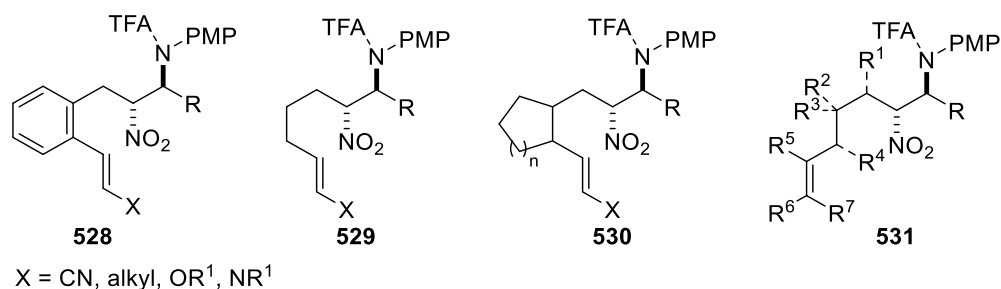
Extension of the methodology to the radical cyclisation of alkynyl-tethered  $\beta$ -nitroacetamides was less successful, with the isolation of indanes **516** proving difficult. Formation of the (*Z*)-alkene **516** was observed where X = TMS, translocation was also observed in this case; a crystal structure of alkene **518** was obtained.



**Scheme 202.** Radical cyclisation of alkynyl-tethered  $\beta$ -nitroacetamides **102xa**

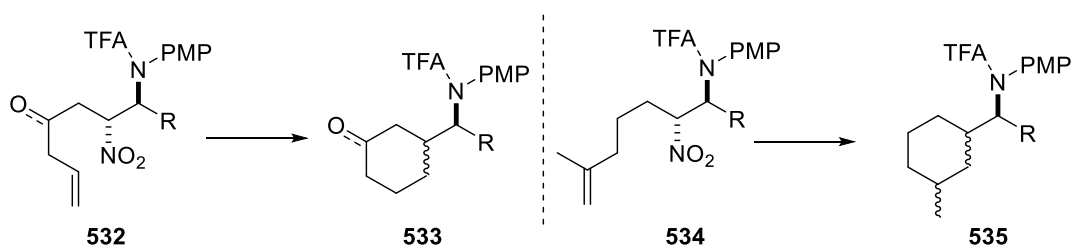
### 2.3.15.1 Future work

The extension of this work to a wider range of tethers could be attempted, with the formation of alkenyl tethers **528** via aldehyde **102al** (**Scheme 173**) and therefore investigation of a wider range of styryl or hexenyl  $\beta$ -nitroacetamides in radical denitration. In addition, a range of non-aromatic tethers could be installed (**530**,  $n = 1, 2, 3$ ), and further investigation of radical cyclisation of electron-poor/electron rich alkenes (**Fig. 33**).



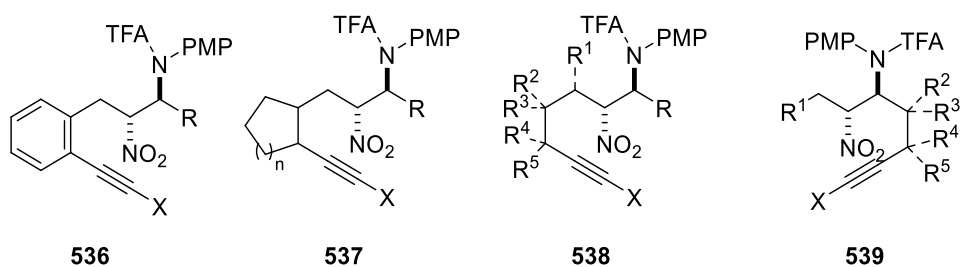
**Fig. 33.** Possible tether modifications in future work – tethers shown as alkene-derived but could be attempted on imine portion

Modification of the alkenyl tethers could also be attempted to induce 6-*endo*-trig cyclisation to afford cyclohexane and tetralyl-type products (**Scheme 203**). Substitution of the 5-hexen-1-yl radical at C-5 (**534**) is known to increase the yield of cyclohexane product (98:2 to 36:64 *exo:endo-cyc*); an increase in the 6-*endo*-cyclisation can also be afforded by substitution of the 5-hexen-1-yl tether with a ketone **532** (up to >97:3 *endo:exo-cyc*).<sup>165</sup>



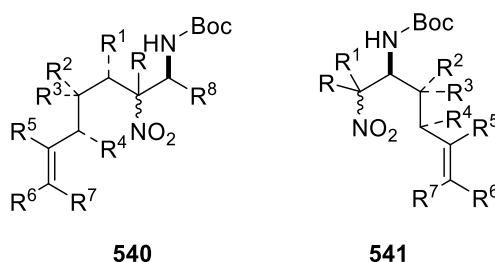
**Scheme 203.** Possible modifications of the 5-hexen-1-yl type tether to induce 6-*endo*-cyclisation

Extension of the alkynyl tethered  $\beta$ -nitroacetamide **536** cyclisations could be extended by differing substitution of the alkyne **536**, or less rigid (**538** & **539**) or aliphatic (**537**-**539**) alkyne tethers could be used, and extension to the imine portion of the  $\beta$ -nitroacetamide **539** (**Fig. 34**).



**Fig. 34.** Further development of the alkynyl tether

A further extension of the radical denitration could investigate the use of an alternative *N*-protecting group. The *N*-allyl group was used to provide substitution of the 5-hexen-1-yl radical tether at C-3 (**Table 27**), however cyclisation occurred in low yield. Use of *N*-Boc imines may prove useful in the formation of tertiary-nitro  $\beta$ -nitroamides **540** & **541**, which in this work proved elusive, presumably due to steric bulk in the molecule (**Fig. 35**). As *N*-Boc protection will obviate TFA-protection, they may be directly submitted to radical cyclisation at high temperatures, formation of tertiary-nitro group  $\beta$ -nitroamides is known<sup>265</sup>



**Fig. 35.** Tertiary nitro alkenyl tethered  $\beta$ -nitroamides

### 2.3.16 Intermolecular radical addition to alkenes

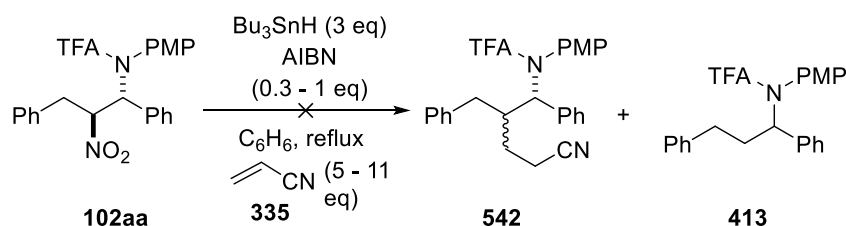
#### 2.3.16.1 Overview

As shown in the previous section, radical denitration and intramolecular radical cyclisation of a range of differentially substituted alkenyl and alkynyl tethers was achieved. Intermolecular addition of carbon radicals to alkenes or alkynes however is known to be more complex. In addition to the considerations required for balancing the rate of hydrogen abstraction ( $k_{\text{abs}}$ ) and the rate of cyclisation ( $k_{\text{cyc}}$ ), for intramolecular addition to an alkene or alkyne, intermolecular addition includes the possibility of further addition of the radical-adduct to a second or third alkene (telomerisation). The intermolecular addition of carbon radicals to alkenes is thus a delicate process, it is known that radical precursor groups (e.g. I/Br/SeR/NO<sub>2</sub>) which do not undergo radical formation at a sufficient rate cannot be used, as preferential addition of the Bu<sub>3</sub>Sn• radical to the alkene occurs.<sup>172</sup> The use of tertiary nitro compounds for intermolecular addition to alkenes has been described<sup>146, 174-176</sup> (see section 1.4.8) with yields of ~ 30 – 70 %, however the use of secondary nitro groups as radical precursors for intermolecular addition to alkenes has not been reported. This was surprising given the claim that activated secondary nitro groups can be denitrated under the same conditions as tertiary nitro groups.<sup>238</sup>



### 2.3.16.2 Attempted intermolecular radical addition of unactivated secondary $\beta$ -nitroacetamides to alkenes

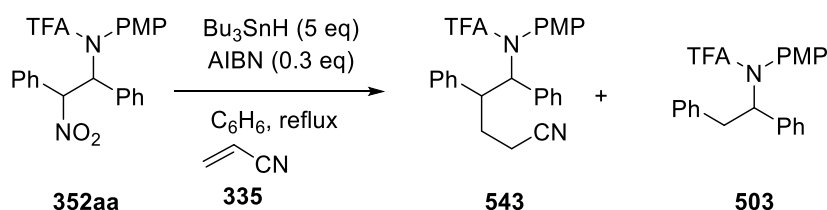
For successful intermolecular radical addition to alkenes, the radical generating group (in this case secondary nitro) must react with tin radical  $\text{Bu}_3\text{Sn}\bullet$  in preference to the reaction of the tin radical with the alkene. The groups stated as unreactive for this type of process due to the slow abstraction of the radical precursor X include ‘most alkyl chlorides, primary and secondary nitro groups and isocyanides’ due to their slow reduction by TBTH.<sup>172</sup> Thus the reaction of secondary nitro compounds in intermolecular carbon-carbon bond formation reactions was deemed to be unlikely. We decided to attempt this reaction under the conditions described by Ono,<sup>146</sup> to definitively ascertain whether these reactions were not possible. In order to increase the likelihood of addition of the secondary radicals to alkenes, frontier molecular orbital effects and sterics were considered. The radical generated from denitration would be nucleophilic due to donation of electron density from the adjacent alkyl chains via hyperconjugation, hence matching the nucleophilic SOMO with an electron deficient alkene would lead to good orbital energy matching with the low lying alkene LUMO. In addition, it is known that the substitution of alkenes at the position of 1,4-addition can result in a slowing of rate due to steric hindrance. Hence acrylonitrile was chosen as the alkene partner. The secondary nitro compound chosen was  $\beta$ -nitroacetamide **102aa** which had been previously prepared and did not contain other functional groups which could be reduced by TBTH. Unfortunately under all conditions attempted (TBTH 3 eq, AIBN 0.3 – 1 eq, **335** 5 – 11 eq), no desired product was observed, only mixtures of starting material **102aa** and some denitration product **413**. Addition of TBTH was via syringe-pump, and addition of AIBN either as one portion or via syringe-pump, this kept the concentration of TBTH low in order to prevent formation of **413**. Use of 11 eq acrylonitrile proved unsuccessful, however a lowering in eq was also unsuccessful. It would appear that under the conditions, due to the slow abstraction of the nitro group, the chain could not be effectively propagated and side reactions dominated, including polymerisation of the alkene.



**Scheme 204.** Attempted radical intermolecular addition of secondary nitro compound **102aa** to acrylonitrile **335**

### 2.3.16.3 Intermolecular radical addition of activated secondary $\beta$ -nitroacetamides to alkenes

With the lack of success with unactivated secondary  $\beta$ -nitroacetamide **102aa**, it was hoped that a more activated nitro compound may prove more successful. Activation of the nitro group by an aromatic ring had increased the protodenitration yield of  $\beta$ -nitroacetamide **352aa** at only 5 eq TBTH to 55 % (0.3 eq AIBN, benzene). It was thought that the addition of the TBTH via syringe-pump and the addition in one portion of acrylonitrile to the reaction may lead to the isolation of the desired adduct of intermolecular addition **543** (Table 37).



**Table 37.** Radical intermolecular addition of activated secondary nitro compound **352aa**

Entry <sup>a</sup>	335 eq	Time	503:543:544 <sup>c</sup>	% Yield 543 <sup>d</sup>
<b>1</b> <sup>b</sup>	5	5 h	100:0:0	-
<b>2</b>	5	o/n	100:0:0	-
<b>3</b>	10	o/n	55:30:15	25
<b>4</b> <sup>b</sup>	10	5 h	75:10:15	-
<b>5</b>	50	5 h	<b>503</b> & polymer	-

<sup>a</sup>Bu<sub>3</sub>SnH added via syringe-pump <sup>b</sup>Bu<sub>3</sub>SnH added in one portion <sup>c</sup>Crude ratio <sup>d</sup>Isolated yield **544** = unidentified

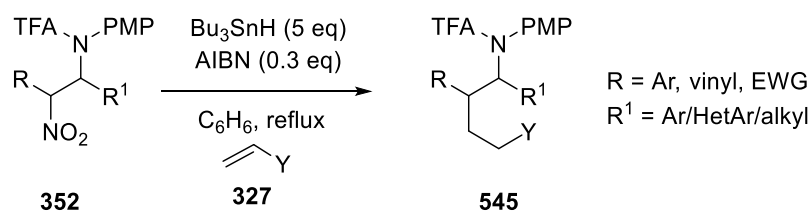
Attempted radical intermolecular addition of activated secondary  $\beta$ -nitroacetamide **352aa** was performed with 5 eq TBTH and 0.3 eq AIBN. Use of 5 eq alkene **335** gave conversion to protodenitration product **503**, both with TBTH added in one portion or via syringe-pump addition (Entries 1 & 2, **Table 37**). To our delight, an increase in the equivalents of alkene **335** from 5 to 10 resulted in the formation of product **543** in 30 % conversion and 25 % isolated yield (Entry 3). Whilst this was not a high yield, low yields in the use of tertiary nitro compounds (from 36 – 62 %, addition to an electron withdrawn alkene)<sup>146</sup> were reported by Ono, and no previous reports of activated secondary nitro compounds were known. An unidentified product **544** (~ 15 % conversion by crude  $^1\text{H}$  NMR) was also seen by  $^1\text{H}$  NMR however it could not be isolated, it was possible that this compound was a second diastereoisomer of the acrylonitrile adduct **543**. Interestingly, it appeared that addition of TBTH in one portion (Entry 4) also resulted in the formation of product **543**, although the conversion was lower, with more protodenitration observed. Further increasing the alkene quantity resulted in the formation of a large amount of polymer, and protodenitration (Entry 5). Characterisation of acrylonitrile adduct **543** was performed by mass spec analysis, confirming the molecular ion peak at 453 (97 %,  $\text{M} + \text{H}^+$ ). The loss of the  $\text{NO}_2$  group was confirmed by IR (no N-O peaks),  $^1\text{H}$  &  $^{13}\text{C}$  NMR showed a loss of the signals for  $\text{CHNO}_2$  at  $\delta$  6.33 ppm and  $\text{CNO}_2$  at  $\delta$  90.3 ppm and a decrease in deshielding of the  $\text{CHN}$  proton from  $\delta$  6.76 ppm to 5.94 ppm, corresponding to loss of the strongly deshielding  $\text{NO}_2$ . The presence of the  $\text{CH}_2\text{CH}_2\text{CN}$  chain was confirmed by the presence of new alkyl peaks at  $\delta$  1.58 ppm (1H, m,  $\text{CH}_2\text{CH}_2\text{CN}$ ) 1.85 ppm (1H, m,  $\text{CH}_2\text{CH}_2\text{CN}$ ) 1.94 ppm (1H, ddd,  $J = 16.8, 9.6, 7.2$ ,  $\text{CH}_2\text{CH}_2\text{CN}$ ) and 2.09 ppm (1H, ddd,  $J = 16.8, 7.2, 4.5$ ,  $\text{CH}_2\text{CH}_2\text{CN}$ ) by  $^1\text{H}$  NMR, corresponding to peaks at  $\delta$  30.4 ppm ( $\text{CH}_2\text{CH}_2\text{CN}$ ) and 15.1 ppm ( $\text{CH}_2\text{CN}$ ). Confirmation of the nitrile functional group was made by IR ( $2245\text{ cm}^{-1}$ , C-N) and  $^{13}\text{C}$  NMR, with a peak at  $\delta$  119.2 ppm corresponding to CN. Acrylonitrile adduct **543** was isolated as a single diastereoisomer, however non-isolated product **544** was thought to be a possible second diastereoisomer, this could not be confirmed. Assignment of the relative orientation of **543** was not possible due to free rotation about the C-CHN bond; due to lack of material isolated, further reaction to form a cyclic compound for assignment of the relative stereochemistry was not attempted. Interestingly, attempts to scale-up the reaction proved unsuccessful. It became clear that formation of **543** was only possible when the reaction was run in a semi-sealed tube. Reinforced microwave-proof sample vials with PTFE-sealed caps allowed the addition of TBTH via syringe pump in the presence of an argon atmosphere, with refluxing

benzene cooled by the walls of the glass vessel. Reactions conducted at reflux in a typical reflux setup, with a round-bottomed flask and condenser were unsuccessful at every attempt. It was hypothesised that this may be partly due to loss of the volatile acrylonitrile. It is known that radical intermolecular addition to alkenes proceeds with low to no diastereoselectivity unless an inherent restriction of conformation of the radical favours preferential addition at the less hindered face.<sup>238</sup> In this case, low diastereoselectivity was expected, however this cannot be definitively confirmed as unknown product **544**, which may be a second diastereoisomer, could not be isolated. Extension to other alkenes was briefly attempted, with methyl acrylate, however the reaction was not performed in a semi-sealed microwavable glass vial, hence this could be the cause of the failure of the reaction. The reaction was not repeated due to lack of time.

### 2.3.17 Intermolecular addition to alkenes: conclusions and future work

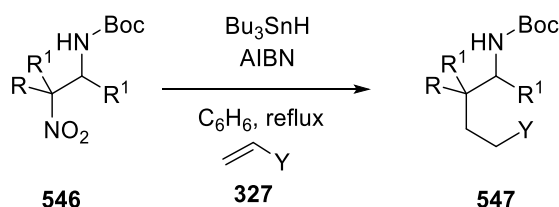
This chapter detailed the attempted radical intermolecular addition of both unactivated (**102aa**) and activated (**352aa**)  $\beta$ -nitroacetamides to acrylonitrile. Despite a lack of success for the unactivated nitro compound **102aa**, activation of the nitro group by use of an adjacent aromatic ring enabled intermolecular addition of the carbon radical formed to acrylonitrile, generating product **543** in low yield. Although this was a low yield, it was the first observed intermolecular addition of a secondary nitro compound to an alkene, and secondary nitro groups are harder to denitrate; tertiary nitro groups add to alkenes in only moderate to good yields (~ 30 – 60 %).<sup>146</sup>

It was found that the reaction was successful only when performed in semi-sealed microwaveable PTFE-capped glass vials. The lack of larger vials hindered scaling up of the reaction, rendering purification difficult. Future work on a larger scale in large vials should aid in isolation of unknown product **544**, which may be a second diastereoisomer. This would be important in obtaining a definitive *dr* for the reaction. In addition, future work could probe a range of partner alkenes **327**, leading to a range of adducts **545** (Scheme 205). This could be conducted with various activated secondary  $\beta$ -nitroacetamides **352** where R = activating group.



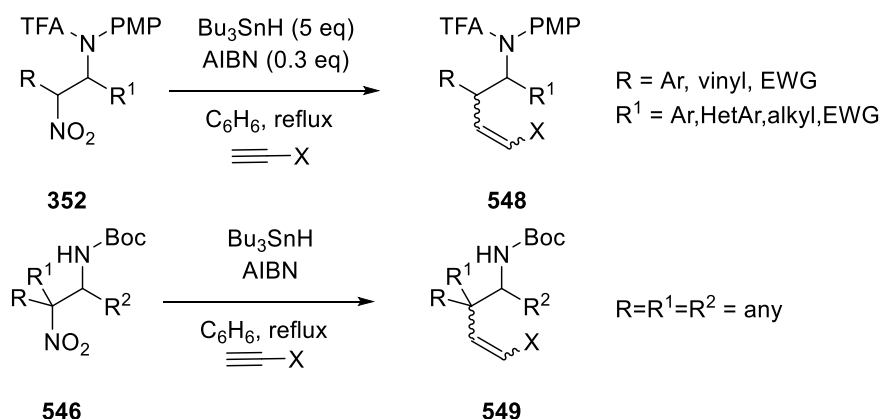
**Scheme 205.** Intermolecular radical addition of  $\beta$ -nitroacetamides **352** to various alkenes

As previously suggested for future work in intramolecular cyclisations, formation of tertiary  $\beta$ -nitroacetamides **546** may be possible with mono-Boc-protection of the amine. Intermolecular radical addition of these tertiary nitro compounds to alkenes should prove higher yielding, and a lower concentration of TBTH would be required (**Scheme 206**).



**Scheme 206.** Intermolecular radical addition of tertiary  $\beta$ -nitroacetamides **546** to alkenes

Due to the slower rate of addition of carbon radicals to alkynes (*c.f.* alkenes),<sup>137b</sup> addition of activated secondary  $\beta$ -nitroacetamides may prove less successful, however it would lead to the generation of useful alkene-adducts **548**. Tertiary nitro  $\beta$ -nitroacetamides **546** could also be subjected to intermolecular radical addition to alkynes; the faster rate of denitration of tertiary nitro compounds would likely lead to a higher yielding reaction, and the ability to use a low concentration of TBTH.

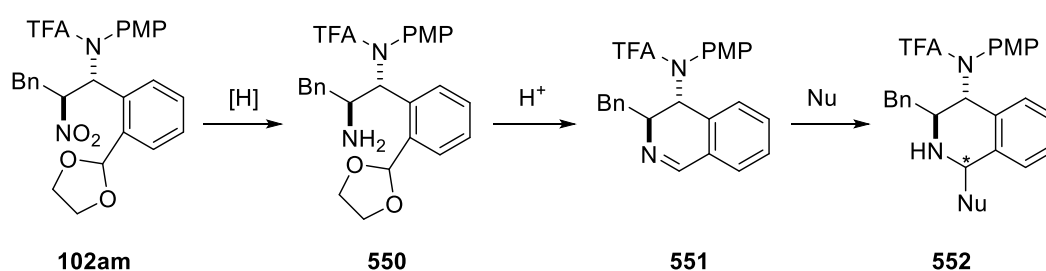


**Scheme 207.** Intermolecular radical addition of activated secondary or tertiary  $\beta$ -nitroacetamides to alkynes

## 2.4 Miscellaneous Reactions

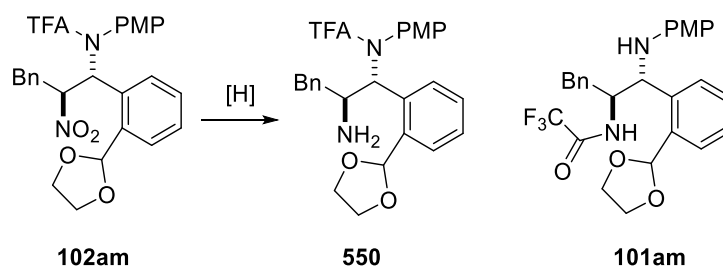
### 2.4.1 Formation of a cyclic imine to give 4-aminotetrahydroisoquinolines

During the generation of starting materials for radical cyclisation reactions, the formation of acetal **102am** was performed, followed by deprotection to give aldehyde **102al** and subsequent alkene formation (**Table 23** & **Scheme 173**). Reduction of the nitro group of acetal **102am** would generate amine **550**, deprotection of the acetal should result in imine **551** formation. It was thought that a range of 1,3-substituted-4-aminotetrahydroisoquinolines **552** could be formed with high diastereoselectivity via nucleophilic addition to imine **551** (**Scheme 208**).



**Scheme 208.** Manipulation of  $\beta$ -nitroacetamides for the formation of tetrahydroisoquinolines

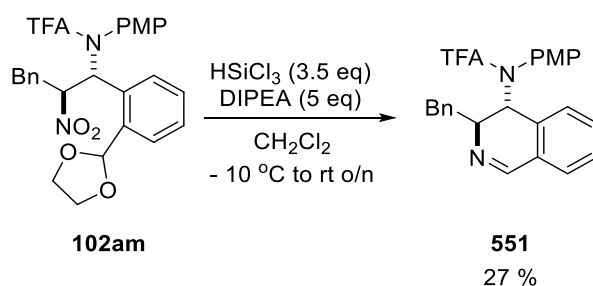
The reduction of  $\beta$ -nitroamines and their derivatives for the preparation of 1,2-diamines has been extensively explored, initial screening for reduction of the nitro group focussed around these methods. Reduction of the nitro group using Raney-Ni/ $HCOOH$ ,<sup>266</sup>  $H_2$ , Pd/C,  $NiCl_2 \cdot 6H_2O/NaBH_4$ ,<sup>88f</sup>  $Zn/HCl$ <sup>65</sup> and were first explored (**Scheme 209**).



**Scheme 209.** Reduction of the nitro group of **102am**

Use of Raney-Ni/ $HCOOH$ <sup>266</sup> proved unsuccessful, resulting in recovered starting material, as did the hydrogenation over Pd/C catalyst (10 mol %). Use of  $Zn/HCl$  in EtOH/EtOAc as previously described in this group<sup>65</sup> resulted in a complex mixture, including some deprotection of the acetal under the acidic conditions. Use of nickel boride, generated using  $NiCl_2 \cdot 6H_2O/NaBH_4$ <sup>88f</sup> proceeded to reduce the nitro compound with translocation of the TFA protecting group *in situ* as previously observed for the

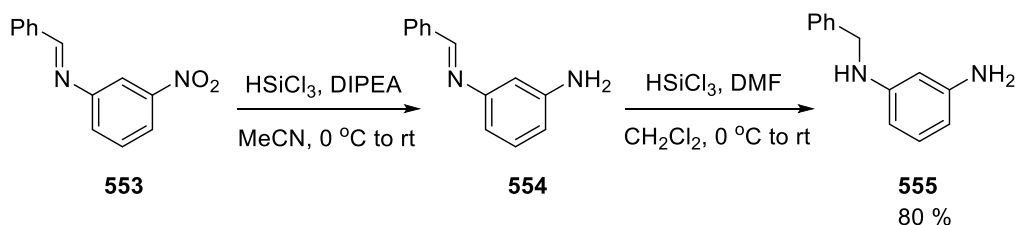
reduction of  $\beta$ -nitroacetamides to give differentially protected 1,2-aminoacetamide **101am** in 36 % yield. Attempted direct reduction of the unprotected  $\beta$ -nitroamine **357am** used crude *in situ* from the nitro-Mannich reaction with  $\text{SmI}_2$ <sup>5</sup> proved unfruitful, giving a complex mixture. A recent paper had detailed the selective reduction of the nitro group in the presence of an imine using  $\text{HSiCl}_3/\text{DIPEA}$ .<sup>70d, 267</sup> To our delight, subjection of **102am** to these reaction conditions resulted in the direct formation of imine **551**, with ~ 66 % conversion, however purification proved problematic, giving a yield of 27 % on purification using silica column chromatography. A switch to alumina for column chromatography did not increase the yield, but resulted in a yield of 19 %, it appeared that the product was decomposing during purification.



**Scheme 210.** Direct formation of imine **551** from **102am**

#### 2.4.2 Conclusions and further work

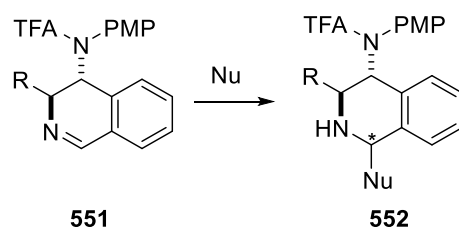
Unfortunately due to a lack of time, further improvements in yield of imine **551** could not be attempted, however the use of the  $\text{HSiCl}_3/\text{DIPEA}$  system proved effective, with direct formation of **551** from  $\beta$ -nitroacetamide **102am**. As previously stated, reduction of a nitro group in the presence of an imine<sup>267</sup> had been performed using the  $\text{HSiCl}_3/\text{DIPEA}$  system (**Scheme 211**).<sup>70d</sup>



**Scheme 211.** One-pot nitro reduction followed by imine reduction<sup>267</sup>

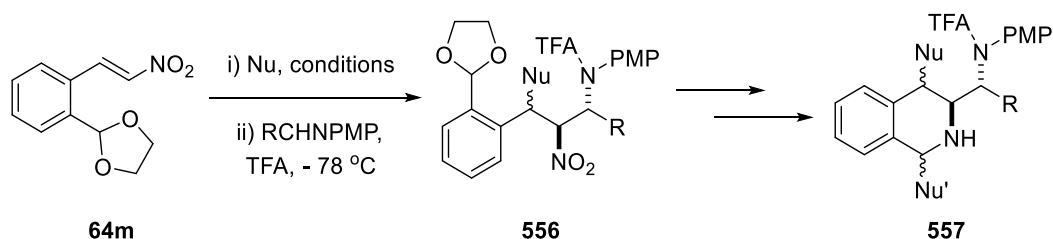
A one-pot reduction of **551** using  $\text{HSiCl}_3/\text{DMF}$  could then be performed, negating its purification, and the subsequent loss in yield. Alternatively, nucleophilic addition to **551** would give rise to a range of 1,3-substituted-4-aminotetrahydroisoquinolines **552**,

substitution at the 3-position (R) could be varied by a variation of nitroalkenes (**Scheme 212**). The presence of two chiral centres on the 3,4-dihydroisoquinoline ring should lead to stereochemical induction in the installation of the nucleophile at C-1.



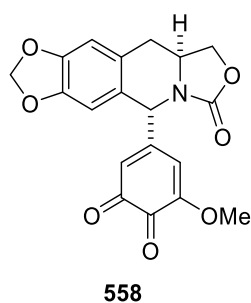
**Scheme 212.** Formation of 1,3,4-substituted tetrahydroisoquinolines **552**

Further work in this area could also include the attachment of the acetal to the nitroalkene portion. In this way, 1,4-conjugate addition of nucleophiles to the nitroalkene followed by nitro-Mannich reaction could generate  $\beta$ -nitroacetamides **556**, which could undergo imine formation and attack as previously stated (**Scheme 213**). This would lead to a range of alternative tetrahydroisoquinolines **557**, with variable substitution at the 1 & 4-positions.



**Scheme 213.** Formation of 1,3,4-substituted tetrahydroisoquinolines from the nitroalkene moiety

Similar substituted tetrahydroisoquinolines are known to possess biological activity, for example the 2-aza analogue of podophyllotoxin, **558** is a potent antitumour agent (**Fig. 36**).<sup>268</sup> Synthesised 1,3,4-substituted tetrahydroisoquinolines **552** or **557** could be subjected to biological screening to determine if they are biologically active compounds.



**Fig. 36.** A 2-azapodophyllotoxin analogue



## Chapter 3: Experimental section

### 3.1 General experimental details

All anhydrous chemistry was performed using a Schlenck apparatus and standard syringe techniques; all glassware was flame-dried and reactions were conducted under an inert atmosphere (argon or nitrogen). Room temperature (rt) denotes a value of 20 – 25 °C, and any temperatures stated reflect the temperature of the external heating/cooling environment. Reaction cooling to 0 °C was performed in an ice-water bath, to – 20 °C in an ice-salt bath, to – 40 °C with a dry ice/acetonitrile bath, and temperatures of – 78 °C were obtained usually by a dry ice/acetone bath, or a liquid nitrogen/EtOAc bath. Thin layer chromatography was carried out using Polygram® SIL G/UV254 0.25 mm silica backed TLC plates, with visualisation by UV light (254 nm) and KMnO<sub>4</sub> or anisaldehyde dip. Flash column chromatography was performed using Gedran® silica gel 60, 40 – 63 µm; the solvent system used is stated in each case. Removal of solvents *in vacuo* was performed using Büchi rotary evaporators with the house vacuum, diaphragm or Vacuubrand vacuums.

All <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR data were obtained using Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz or Bruker AVANCE III 600 MHz machines, at room temperature unless stated. Data was manipulated directly using TopSpin (3.2). Unless otherwise stated, NMR data was obtained as a dilute solution in CDCl<sub>3</sub>, chemical shifts (δ) are reported in parts per million (ppm) relative to the solvent peak values of δ = 7.26 ppm (<sup>1</sup>H NMR) and 77.1 ppm (<sup>13</sup>C NMR) for CDCl<sub>3</sub>. Multiplicities are reported as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br refers to a broad signal, apt = apparent. Coupling constants (*J*) are measured in Hertz (Hz). Where appropriate, additional NMR techniques have been used to aid assignment (COSY, DEPT, HSQC, HMBC and NOE experiments). Mass spectroscopy analysis data were collected using Thermo Finnigan Mat900xp (EI/CI) or Waters LCT premier XE (ESI) machines. Infrared data were collected on a Shimadzu 8700 FT-IR machine as a neat sample (thin film). Elemental analysis was carried out on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are reported uncorrected, and were recorded on a Griffin melting point apparatus.

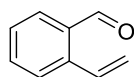
## 3.2 Purification of laboratory reagents

With the exception of specifically mentioned examples, all commercial reagents and solvents detailed were used as supplied or purified by the standard techniques described.<sup>269</sup> The concentration of commercially-sourced organolithium reagents was verified by titration with *N*-benzylbenzamide at  $-40\text{ }^{\circ}\text{C}$ .<sup>270</sup> Dry dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), diethyl ether ( $\text{Et}_2\text{O}$ ), toluene, tetrahydrofuran (THF) or hexanes were obtained from a solvent tower, in which degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Purification and drying of alcohols, aldehydes, amines or alkenes was carried out via standard procedures, and the resultant purified substances stored under argon at the correct temperature.<sup>269</sup> Benzene used for radical reactions was purified to remove traces of thiophene as described.<sup>269</sup> Recrystallisation of AIBN (2,2'-azobis(2-methylproionitrile)) was carried out from  $\text{Et}_2\text{O}$ , the reagent was stored under argon between  $-5$  and  $-20\text{ }^{\circ}\text{C}$ . Diiodoethane was washed with sodium thiosulfate solution, dried and stored under argon at  $-20\text{ }^{\circ}\text{C}$ . Activation of 3 or 4 Å molecular sieves was performed via heating under high vacuum.

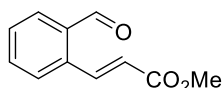
## 3.3 Synthetic procedures and characterisation

### 3.3.1 Preparation of aldehydes

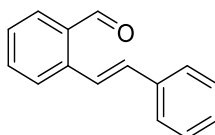
#### 2-vinylbenzaldehyde (358d)



To a solution of 2-bromostyrene (7.80 g, 42.6 mmol) in dry THF (130 mL) under  $\text{N}_2$  at  $-78\text{ }^{\circ}\text{C}$  was added dropwise a solution of  $n\text{BuLi}$  (1.1 M in hexanes, 48 mL, 53 mmol). The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 1 h followed by the addition of dry DMF (5.00 mL, 64.8 mmol) and the reaction stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 h before warming to rt. The reaction mixture was diluted with  $\text{Et}_2\text{O}$  (200 mL), washed with brine (200 mL x 2) dried ( $\text{MgSO}_4$ ) filtered and concentrated *in vacuo*. Purification by flash column chromatography (2 – 10 %  $\text{EtOAc}$ /Petroleum ether) afforded **358d** as a colourless oil (4.44 g, 33.6 mmol, 80 %);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz) 5.49 (1H, apt d,  $J = 11.0$ ,  $\text{ArCHCH}_{2\text{-trans}}$ ) 5.69 (1H, apt d,  $J = 17.3$ ,  $\text{ArCHCH}_{2\text{-cis}}$ ) 7.42 (1H, m,  $\text{ArCHCH}_2$ ) 7.49 – 7.57 (3H, m,  $\text{ArH}$ ) 7.81 (1H, d,  $J = 7.7$  Hz,  $\text{ArH}$ ) 10.27 ppm (1H, s,  $\text{CHO}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  119.5 ( $\text{CH}_2$ ) 127.6 ( $\text{ArC}$ ) 128.0 ( $\text{ArC}$ ) 131.4 ( $\text{ArC}$ ) 132.9 (q,  $\text{ArCCHO}$ ) 133.5 ( $\text{ArC}$ ) 134.0 ( $\text{CHCH}_2$ ) 140.6 (q,  $\text{ArCCHCH}_2$ ) 192.5 ( $\text{CHO}$ ). NMR data is consistent with published data.<sup>271</sup>

**methyl (*E*)-3-(2-formylphenyl)acrylate (358e)**

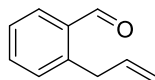
A mixture of degassed methyl acrylate (7.00 mL, 77.7 mmol), Pd(OAc)<sub>2</sub> (0.23 g, 1.02 mmol) PPh<sub>3</sub> (0.55 g, 2.10 mmol) and 2-bromobenzaldehyde (6.00 mL, 51.4 mmol) in degassed NEt<sub>3</sub> (19 mL) was heated to reflux under Ar o/n. The reaction was cooled and concentrated *in vacuo*. To this was added H<sub>2</sub>O (100 mL) and the mixture was filtered. The filtrate was extracted with EtOAc (100 mL x 3) washed with 2M HCl (200 mL) brine (200 mL) dried (MgSO<sub>4</sub>) filtered and concentrated. *in vacuo*. Purification by flash column chromatography (10 % EtOAc/Hexanes) afforded **358e** as a yellow oil (4.23 g, 22.2 mmol, 45 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 3.83 (3H, s, COOCH<sub>3</sub>) 6.38 (1H, d, *J* = 15.9, ArCHCHCO<sub>2</sub>CH<sub>3</sub>) 7.54 – 7.69 (3H, m, ArH) 7.87 (1H, d, *J* = 7.5, ArH) 8.53 (1H, d, *J* = 16.2, ArCHCHCO<sub>2</sub>CH<sub>3</sub>) 10.28 (1H, s, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 52.1 (OCH<sub>3</sub>) 122.8 (CHCO<sub>2</sub>CH<sub>3</sub>) 128.1 (ArC) 130.1 (ArC) 132.6 (ArC) 133.9 (q, ArCCHCH) 134.1 (ArC) 136.6 (q, ArCCHO) 141.4 (CHCHCO<sub>2</sub>CH<sub>3</sub>) 166.8 (CO<sub>2</sub>CH<sub>3</sub>) 192.0 (CHO). NMR data is consistent with published data.<sup>272</sup>

**(*E*)-2-styrylbenzaldehyde (358g)**

To a mixture of 2-bromobenzaldehyde (2.90 mL, 24.8 mmol), K<sub>3</sub>PO<sub>4</sub> (8.14 g, 38.3 mmol) and styrene (30.0 mL, 250 mmol) in DMA (50 mL) under N<sub>2</sub> was added Pd(OAc)<sub>2</sub> (89.7 mg, 0.14 mmol) and the reaction was stirred at reflux for 1 h. The reaction mixture was cooled and poured into ice-water (100 mL), filtered through celite, extracted with EtOAc (200 mL x 3), washed with brine (350 mL) dried (K<sub>2</sub>CO<sub>3</sub>) filtered and concentrated *in vacuo*. Purification by flash column chromatography (25 % PhCH<sub>3</sub>/Hexanes) afforded **358g** as a yellow oil (3.81 g, 18.3 mmol, 74 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 7.07 (1H, d, *J* = 16.2, CH) 7.32 (1H, m, ArH) 7.40 (2H, m, ArH) 7.45 (1H, td, *J* = 7.6, 0.7, ArH) 7.57 – 7.62 (3H, m, ArH) 7.74 (1H, d, *J* = 7.8, ArH) 7.86 (1H, dd, *J* = 7.8, 1.3, ArH) 8.07 (1H, d, *J* = 16.2, CH) 10.34 (1H, s, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 124.9 (CH) 127.1 (2C, ArC) 127.3 (2C, ArC) 127.8 (ArC) 128.5 (ArC) 128.9 (ArC) 132.5 (ArC)

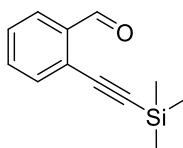
133.0 (q, ArC) 133.9 (CH) 134.1 (ArC) 137.0 (q, ArC) 140.1 (q, ArC) 192.9 (CHO). NMR data is consistent with published data.<sup>273</sup>

### 2-allylbenzaldehyde (358u)



To a solution of acetal **504** (7.80 g, 41.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (600 mL) was added FeCl<sub>3</sub>·6H<sub>2</sub>O (41.0 g, 150 mmol) and the reaction was stirred at rt until complete by TLC analysis. The reaction was quenched with sat. aq. NaHCO<sub>3</sub> solution (1 L) and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1 L x 3), the combined organic extracts were washed with brine (3 L), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*, affording crude aldehyde **358u** as a colourless oil, used without further purification (6.00 g, 41.0 mmol, 100 %); R<sub>F</sub> = 0.69 (15 % EtOAc/Petroleum ether); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 3.83 (2H, d, *J* = 6.1, ArCH<sub>2</sub>) 4.99 (1H, d, *J* = 17.1, ArCH<sub>2</sub>CHCH<sub>2-trans</sub>) 5.10 (1H, d, *J* = 10.1, ArCH<sub>2</sub>CHCH<sub>2-cis</sub>) 6.04 (1H, ddt, *J* = 17.0, 10.4, 6.2, ArCH<sub>2</sub>CH) 7.30 (1H, d, *J* = 7.5, ArH) 7.41 (1H, t, *J* = 7.5, ArH) 7.54 (1H, t, *J* = 7.5, ArH) 7.86 (1H, d, *J* = 7.7, ArH) 10.3 (1H, s, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 36.7 (ArCH<sub>2</sub>) 116.6 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 127.1 (ArC) 131.2 (ArC) 131.7 (ArC) 133.9 (q, ArCCHO) 134.1 (ArC) 137.1 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 142.4 (q, ArCCH<sub>2</sub>) 192.5 (CO). NMR data is consistent with published data.<sup>274</sup>

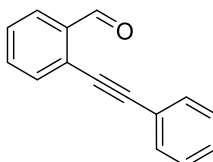
### 2-(trimethylsilylethynyl)benzaldehyde (358v)



To a solution of CuI (48.0 mg, 0.25 mmol, 1 mol %) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (339 mg, 0.48 mmol, 2 mol %) in degassed NEt<sub>3</sub> (60 mL) at rt under N<sub>2</sub> was added 2-bromobenzaldehyde (2.80 mL, 24.0 mmol) followed by addition of TMS-acetylene (4.20 mL, 29.7 mmol) and the reaction mixture was heated to 50 °C. The reaction was stirred at 50 °C for 3 h until complete, then concentrated *in vacuo*. Purification by flash column chromatography (2-10 % EtOAc/hexanes) afforded **358v** as an off-white solid (4.24 g, 21.0 mmol, 88 %) mp 50 – 52 °C (lit<sup>275</sup> 50 – 52 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 0.28 (9H, s, CH<sub>3</sub>) 7.44 (1H, t, *J* = 7.6, ArH) 7.54 (1H, m, ArH) 7.58 (1H, dd, *J* = 8.0, 1.1, ArH) 7.91 (1H, dd, *J* = 7.9, 0.8, ArH) 10.56 (1H, s, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ –

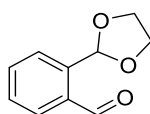
0.17 (3C, Si(CH<sub>3</sub>)<sub>3</sub>) 100.1 (q, CCSi) 102.5 (q, CSi(CH<sub>3</sub>)<sub>3</sub>) 126.9 (q, ArCCHO) 127.0 (ArC) 128.9 (ArC) 133.6 (ArC) 133.7 (ArC) 136.3 (q, ArCCC) 191.9 (CO). Data is consistent with literature data.<sup>276</sup>

### 2-(phenylethynyl)benzaldehyde (**358w**)



To a solution of CuI (72.4 mg, 0.36 mmol, 1 mol %) and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (505 mg, 0.72 mmol, 2 mol %) in degassed NEt<sub>3</sub> (90 mL) at rt under N<sub>2</sub> was added 2-bromobenzaldehyde (4.20 mL, 36.0 mmol) followed by addition of phenylacetylene (6.00 mL, 54.6 mmol) and the reaction mixture was heated to 50 °C. The reaction was stirred at 50 °C for 1 h before concentration *in vacuo*. Purification by flash column chromatography (2 % EtOAc/Hexanes) afforded **358w** as a yellow oil (6.91 g, 33.5 mmol, 93 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 7.38 – 7.41 (3H, m, ArH) 7.46 (1H, apt tt, *J* = 0.9, ArH) 7.57 – 7.61 (3H, m, ArH) 7.66 (1H, dd, *J* = 7.5, 0.8, ArH) 7.96 (1H, dd, *J* = 7.9, 1.0, ArH) 10.67 (1H, apt d, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 85.0 (q, CC) 96.5 (q, CC) 122.4 (q, ArC) 127.0 (q, ArC) 127.4 (ArC) 128.7 (2C, ArC) 128.8 (ArC) 128.8 (ArC) 129.2 (ArC) 131.8 (ArC) 133.4 (ArC) 133.9 (ArC) 135.9 (q, ArC) 191.9 (CO). NMR data consistent with published data.<sup>277</sup>

### 2-(1,3-dioxolan-2-yl)benzaldehyde (**358m**)



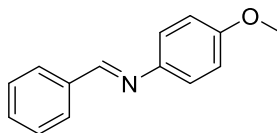
To a solution of aryl bromide **462** (25.0 g, 110 mmol) in dry THF (300 mL) under N<sub>2</sub> at - 80 °C was added dropwise <sup>n</sup>BuLi in Hexanes (1.8 M, 62 mL, 111 mmol) giving an orange colour. The reaction was stirred for 30 min at - 80 °C before dropwise addition of dry DMF (12 mL, 155 mmol), and the solution was allowed to warm to rt. On completion of the reaction by TLC analysis, the reaction mixture was diluted with Et<sub>2</sub>O (300 mL), washed with brine (3 x 500 mL), dried (MgSO<sub>4</sub>) filtered and concentrated *in vacuo*. Purification by flash column chromatography (3-100 % EtOAc/Petroleum ether) afforded **358m** as a colourless oil (15.4 g, 86.6 mmol, 79 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 4.13

(4H, m,  $\text{OCH}_2\text{CH}_2\text{O}$ ) 6.40 (1H, s,  $\text{CHO}_2$ ) 7.53 (1H, td,  $J = 7.7, 1.0$ , ArH) 7.61 (1H, td,  $J = 7.7, 1.4$ , ArH) 7.73 (1H, dd,  $J = 7.7, 1.1$ , ArH) 7.94 (1H, dd,  $J = 7.7, 1.3$ , ArH) 10.41 (1H, s,  $\text{CHO}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  65.5 (2C,  $\text{OCH}_2\text{CH}_2\text{O}$ ) 101.2 ( $\text{CHO}_2$ ) 127.1 (ArC) 129.6 (ArC) 130.3 (ArC) 133.8 (ArC) 134.6 (q, ArC) 139.2 (q, ArC) 192.0 ( $\text{CHO}$ ). NMR data consistent with published data<sup>278</sup>

### 3.3.2 Preparation of imines

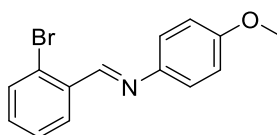
**General procedure A:** A solution of  $\text{Al}_2\text{O}_3$  (1 g per mmol) and *p*-anisidine (1.00 mmol) in dry DCM (5 mL) was stirred at rt under  $\text{N}_2$  for 5 min before the addition of benzaldehyde (1.00 mmol) and the reaction was stirred until complete. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude imine.

#### (*E*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine (**82a**)

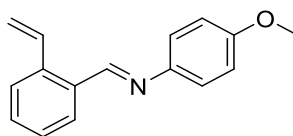


Prepared by *general procedure A* using benzaldehyde (3.10 mL, 31.6 mmol). Purification by recrystallization (EtOAc/Pet. Ether) afforded **82a** as white platelets (4.01 g, 19.0 mmol, 63 %); mp 70 – 71 °C (lit<sup>26</sup> 68 – 70 °C)  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.86 (3H, s,  $\text{OCH}_3$ ) 6.96 (2H, dm,  $J = 8.8$ , ArH) 7.27 (2H, dm,  $J = 8.9$ , ArH) 7.47-7.51 (3H, m, ArH) 7.90-7.93 (2H, m, ArH) 8.51 (1H, s,  $\text{CHNMP}$ ). NMR data is consistent with published data.<sup>279</sup>

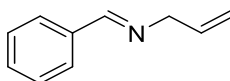
#### (*E*)-1-(2-bromophenyl)-*N*-(4-methoxyphenyl)methanimine (**82b**)



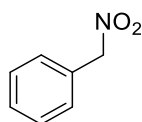
Prepared by *general procedure A* using 2-bromobenzaldehyde (7.04 g, 24.3 mmol). Purification by recrystallisation (EtOAc/Pet. Ether) afforded **82b** as yellow needles (6.12 g, 21.1 mmol, 87 %) mp 65 °C (lit<sup>280</sup> 73 – 74 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.87 (3H, s,  $\text{OMe}$ ) 6.75 (2H, dm,  $J = 8.8$ , ArH) 7.28 – 7.44 (3H, m, ArH) 7.42 (1H, t,  $J = 7.4$ , ArH) 7.63 (1H, dd,  $J = 8.0, 1.2$ , ArH) 8.25 (1H, dd,  $J = 7.6, 1.6$ , ArH) 8.90 (1H, s,  $\text{HCN}$ ). NMR data consistent with published data.<sup>281</sup>

**(E)-N-(4-methoxyphenyl)-1-(2-vinylphenyl)methanimine (82d)**

Prepared using *general procedure A* using aldehyde **358d** (1.00 g, 7.57 mmol) afforded **82d** as a waxy yellow solid used directly without further purification (1.87 g, > 7.6 mmol, quant) mp 32 – 33 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  3.84 (3H, s,  $\text{OCH}_3$ ) 5.45 (1H, apt d,  $J = 11.1$ ,  $\text{ArCHCH}_2\text{-cis}$ ) 6.67 (1H, apt d,  $J = 17.1$ ,  $\text{ArCHCH}_2\text{-trans}$ ) 6.95 (2H, apt d,  $J = 8.2$ , PMP-*H*) 7.24 (2H, apt d,  $J = 8.1$ , PMP-*H*) 7.29 – 7.47 (3H, m, *ArH* &  $\text{ArCHCH}_2$ ) 7.52 (1H, d,  $J = 7.6$ , *ArH*) 8.09 (1H, d,  $J = 7.4$ , *ArH*) 8.83 (1H, s, *HCN*). NMR data consistent with published data.<sup>282</sup>

**(E)-N-allyl-1-phenylmethanimine (82t)**

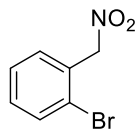
A mixture of benzaldehyde (1.00 mL, 9.81 mmol), allyl amine (0.75 mL, 10.0 mmol) and  $\text{MgSO}_4$  (3.7 g, 30.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was stirred at rt for 18 h. The reaction mixture was filtered through a pad of celite affording **82t** as a colourless oil used directly without further purification (97 % conversion);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  4.28 (2H, dd,  $J = 5.7$ , 1.4,  $\text{NCH}_2$ ) 5.17 (1H, dq,  $J = 10.3$ , 1.5,  $\text{NCH}_2\text{CHCH}_2\text{-cis}$ ) 5.25 (1H, dq,  $J = 17.2$ , 1.6,  $\text{NCH}_2\text{CHCH}_2\text{-trans}$ ) 6.09 (1H, ddt,  $J = 17.1$ , 10.4, 5.7,  $\text{NCH}_2\text{CHCH}_2$ ) 7.40 – 7.45 (3H, m, *ArH*) 7.75 – 7.78 (2H, m, *ArH*) 8.31 (1H, s, *CHN*). NMR data consistent with published data.<sup>283</sup>

**3.3.3 Preparation of nitroalkanes** **$\alpha$ -nitrotoluene (4a)**

To a solution of urea (27.0 g, 0.45 mol) in dry DMF (400 mL) at – 20 °C was added  $\text{NaNO}_2$  (24.0 g, 0.35 mol) followed by  $\text{BnBr}$  (27.0 mL, 0.23 mol) and the reaction was stirred at – 20 °C for 6 h. The reaction mixture was quenched by pouring into ice-water (1 L) and  $\text{Et}_2\text{O}$  (200 mL), separated and extracted with  $\text{Et}_2\text{O}$  (500 mL x 3). The combined

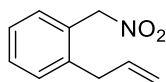
organic extracts were washed with water (500 mL x 4) dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by distillation (93 – 95 °C, 5 mmHg) afforded **4a** as a colourless oil (9.41 g, 68.7 mmol, 30 %); bp 93 – 95 °C (5 mmHg) (lit<sup>284</sup> 99 - 102 °C, 5 mmHg); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  5.44 (2H, s, CH<sub>2</sub>NO<sub>2</sub>) 7.41 – 7.49 (5H, m, ArH). NMR data consistent with published data<sup>285</sup>

### 2-bromo- $\alpha$ -nitrotoluene (**4c**)



To a solution of silver nitrite (6.13 g, 36.1 mmol) in water (20 mL) was added 2-bromobenzylbromide (2.50 g, 10.0 mmol) and the reaction stirred for 18 h. The solution was filtered through a pad of celite using EtOAc as the eluent and the washings partitioned between EtOAc and water. Combined organic extracts were washed with brine (100 mL), dried (MgSO<sub>4</sub>) filtered and concentrated *in vacuo*. Purification by flash column chromatography (50 % toluene/hexane) afforded **4c** as a colourless oil (0.85 g, 3.94 mmol, 39 %); IR  $\nu_{\text{max}}$  (thin film) 1549 (N-O asym) 1471 (C=C, Ar) 1366 (N-O sym) 613 (C-Br) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  5.61 (2H, s, ArCH<sub>2</sub>NO<sub>2</sub>) 7.32 (1H, td,  $J$  = 7.7, 1.8, ArH) 7.40 (1H, td,  $J$  = 7.5, 1.2, ArH) 7.44 (1H, dd,  $J$  = 7.6, 1.8, ArH) 7.66 (1H, dd,  $J$  = 8.0, 1.1, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  79.2 (CH<sub>2</sub>NO<sub>2</sub>) 125.9 (q, ArCBr) 128.2 (ArC) 129.6 (q, ArCCH<sub>2</sub>) 131.8 (ArC) 132.9 (ArC) 133.5 (ArC); m/z (EI) 215 + 217 (1:1, 1 %, M<sup>+</sup>) 168 + 170 (1:1, 68 %, C<sub>7</sub>H<sub>6</sub>Br<sup>+</sup>); HRMS (C<sub>7</sub>H<sub>6</sub>(<sup>79</sup>Br)NO<sub>2</sub>) calcd. 214.9582, found 214.9588.

### 1-allyl-2-(nitromethyl)benzene (**4u**)

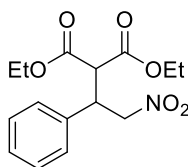


A mixture of bromide **506** (5.30 g, 25.1 mmol) and AgNO<sub>2</sub> (15.4 g, 100 mmol) in water (50 mL) was stirred at rt overnight. When the reaction was complete by TLC, the reaction mixture was filtered through celite and washed through with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (120 mL x 3) washed with brine (300 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20 % Toluene/Hexanes) afforded **4u** as a yellow oil (1.57 g, 8.88 mmol, 36 %); R<sub>F</sub> = 0.20 (20 % Toluene/Hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$



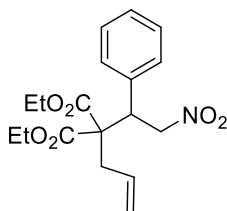
3.51 (2H, d,  $J = 6.1$ ,  $\text{ArCH}_2\text{CHCH}_2$ ) 4.99 (1H, d,  $J = 17.3$ ,  $\text{ArCH}_2\text{CHCH}_2\text{-trans}$ ) 5.12 (1H, d,  $J = 10.2$ ,  $\text{ArCH}_2\text{CHCH}_2\text{-cis}$ ) 5.51 (2H, s,  $\text{CH}_2\text{NO}_2$ ) 5.95 (1H, ddt,  $J = 17.0, 10.2, 6.1$ ,  $\text{ArCH}_2\text{CHCH}_2$ ) 7.28 – 7.33 (2H, m,  $\text{ArH}$ ) 7.38 – 7.43 (2H, m,  $\text{ArH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  37.2 ( $\text{ArCH}_2\text{CHCH}_2$ ) 77.3 ( $\text{CH}_2\text{NO}_2$ ) 116.8 ( $\text{ArCH}_2\text{CHCH}_2$ ) 127.3 ( $\text{ArC}$ ) 128.5 (q,  $\text{ArCCH}_2\text{NO}_2$ ) 130.6 ( $\text{ArC}$ ) 130.7 ( $\text{ArC}$ ) 132.0 ( $\text{ArC}$ ) 136.1 ( $\text{ArCH}_2\text{CHCH}_2$ ) 139.8 ( $\text{ArCCH}_2\text{CHCH}_2$ );  $m/z$  ( $\text{CI}^+$ ) 296 (44%) 212 (14 %,  $\text{M} + 2\text{NH}_3 + \text{H}^+$ ) 195 (100 %,  $\text{M} + \text{NH}_4^+$ ) HRMS ( $\text{C}_{10}\text{H}_{11}\text{NO}_2 + \text{NH}_4^+$ ) calcd. 195.1128, found 195.1127.

**diethyl 2-(2-nitro-1-phenylethyl)malonate (481)**



A mixture of *trans*- $\beta$ -nitrostyrene **64a** (1.00 g, 6.70 mmol) DABCO (0.15 g, 1.34 mmol) and diethyl malonate (3.0 mL, 20 mmol) in THF (7 mL) was stirred at rt under Ar for 3 d then concentrated *in vacuo*. Purification by flash column chromatography (20 – 50 % EtOAc/Hexanes) afforded **481** as a white solid (0.86 g, 2.78 mmol, 41 %); mp 47 - 49 °C (lit<sup>286</sup> 49 – 50 °C); IR  $\nu_{\text{max}}$  (thin film) 1727 (C=O, ester) 1553 (N-O, asym) 1370 (N-O, sym) 1177 (C-O, ester)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  1.03 (3H, t,  $J = 7.1$ ,  $\text{CH}_3$ ) 1.25 (3H, t,  $J = 7.1$ ,  $\text{CH}_3$ ) 3.81 (1H, d,  $J = 9.4$ ,  $\text{CH}(\text{CO}_2\text{Et})_2$ ) 3.99 (2H, q,  $J = 7.1$ ,  $\text{CO}_2\text{CH}_2$ ) 4.17 – 4.25 (3H, m,  $\text{CO}_2\text{CH}_2$  and  $\text{CHCH}_2\text{NO}_2$ ) 4.85 (1H, dd,  $J = 13.1, 9.4$ ,  $\text{CH}_2\text{NO}_2$ ) 4.92 (1H, dd,  $J = 13.0, 4.8$ ,  $\text{CH}_2\text{NO}_2$ ) 7.23 (2H, apt dd,  $J = 7.0, 1.3$ ,  $\text{ArH}$ ) 7.27 (1H, apt d,  $J = 7.2$ ,  $\text{ArH}$ ) 7.30 (2H, m,  $\text{ArH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  13.7 ( $\text{CH}_3$ ) 14.1 ( $\text{CH}_3$ ) 43.1 (PhCH) 55.0 ( $\text{C}(\text{CO}_2\text{Et})_2$ ) 62.0 ( $\text{CH}_2$ ) 62.3 ( $\text{CH}_2$ ) 77.8 ( $\text{CH}_2\text{NO}_2$ ) 128.1 (2C, ArC) 128.5 (ArC) 129.0 (2C, ArC) 136.3 (q, ArC) 167.0 (CO) 167.6 (CO); NMR data consistent with published data.<sup>287</sup>

**diethyl 2-allyl-2-(2-nitro-1-phenylethyl)malonate (4p)**



To a solution of diethyl 2-allylmalonate (1.02 g, 5.10 mmol) in dry THF (35 mL) under argon at rt was added  $^t\text{BuOK}$  (0.48 g, 4.24 mmol). The reaction mixture was cooled to –

40 °C before the addition of a solution of nitrostyrene (1.16 g, 7.76 mmol) in dry THF (5 mL) and the reaction stirred at – 40 °C for a further 1 h . Reaction was quenched with saturated NH<sub>4</sub>Cl solution (50 mL), concentrated. *in vacuo* to remove the organic solvent. The aqueous layer was extracted with EtOAc (90 mL x 3) washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. *in vacuo*. Purification via flash column chromatography (5-25 % EtOAc/Pet. Ether) afforded **4p** as an orange oil (0.97 g, 2.77 mmol, 54 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.26 (3H, t, *J* = 7.0, CH<sub>3</sub>) 1.31 (3H, t, *J* = 7.1, CH<sub>3</sub>) 2.26 (1H, apt dd, *J* = 14.8, 8.0, CCH<sub>2</sub>CHCH<sub>2</sub>) 2.57 (1H, apt ddt, *J* = 14.6, 6.6, 1.4, CCH<sub>2</sub>CHCH<sub>2</sub>) 4.19 (1H, dd, *J* = 11.0, 3.1, CHPh) 4.22 (2H, q, *J* = 7.1, CH<sub>2</sub>CH<sub>3</sub>) 4.27 (1H, dq, *J* = 10.9, 7.1, OCH<sub>2</sub>CH<sub>3</sub>) 4.29 (1H, dq, *J* = 10.9, 7.1, OCH<sub>2</sub>CH<sub>3</sub>) 4.98 (1H, dd, *J* = 13.5, 11.0, CHPhCH<sub>2</sub>NO<sub>2</sub>) 5.05 (1H, apt dq, *J* = 17.0, 1.6, CH<sub>2</sub>CHCH<sub>2-trans</sub>) 5.09 (1H, dd, *J* = 13.5, 3.2, CHPhCH<sub>2</sub>NO<sub>2</sub>) 5.13 (1H, dm, *J* = 10.1, CH<sub>2</sub>CHCH<sub>2-cis</sub>) 5.74 (1H, apt dddd, *J* = 17.0, 10.1, 8.0, 6.6, CCH<sub>2</sub>CHCH<sub>2</sub>) 7.11 – 7.15 (2H, m, ArH) 7.27 – 7.31 (3H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 14.1 (CH<sub>3</sub>) 14.2 (CH<sub>3</sub>) 38.5 (CCH<sub>2</sub>CHCH<sub>2</sub>) 46.7 (CHPh) 60.5 (q, C(COOEt)<sub>2</sub>) 62.1 (2C, COOCH<sub>2</sub>) 78.7 (CH<sub>2</sub>NO<sub>2</sub>) 120.0 (CCH<sub>2</sub>CHCH<sub>2</sub>) 128.6 (ArC) 128.9 (2C, ArC) 129.0 (2C, ArC) 131.9 (CCH<sub>2</sub>CHCH<sub>2</sub>) 135.1 (q, ArC) 169.7 (q, CO) 169.8 (q, CO); *m/z* (CI<sup>+</sup>) 350 (81 %, *M* + H<sup>+</sup>), 303.1 (99%, C<sub>18</sub>H<sub>23</sub>O<sub>4</sub><sup>+</sup>); Data is consistent with part-published data.<sup>288</sup>

### 3.3.4 Preparation of nitroalkenes

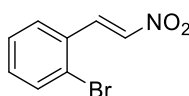
**General procedure B:** To a solution of aldehyde (1.00 mmol) and nitroalkane (2.50 mmol) in methanol (0.5 mL) at 0 °C was added aq. 1M NaOH (2.5 mL) dropwise while maintaining an internal reaction temperature of 10-15 °C. Ice water (1.8 mL) was added and the reaction stirred at 0 °C for 15 min. The reaction mixture was then added to 8 M HCl (1.8 mL, 14.0 mmol) at 0 °C to give a blue colour. The reaction was left to stir overnight giving a yellow colour. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (80 mL x 3), washed with brine (80 mL) dried (MgSO<sub>4</sub>), filtered and conc *in vacuo* to give the crude nitroalkene, which was purified by recrystallisation or flash column chromatography.

**General procedure C:** A solution of nitroalkane (5.00 mmol), triethylamine (0.35 mmol) and aldehyde (1.00 mmol) was stirred overnight under N<sub>2</sub> at rt. Nitroalkane and base removed *in vacuo*; purification by silica plug gave nitroalcohol which was used directly in the next step. Purified nitroalcohol (1.00 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under N<sub>2</sub> and cooled to 0 °C. MsCl (1.20 mmol) was added dropwise and the reaction

stirred for 5 min before dropwise addition of a solution of DIPEA (2.50 mmol) in dry DCM (2 mL). The reaction was stirred at 0 °C until complete before warming to rt. The reaction was washed with H<sub>2</sub>O (5 mL x 2), 2M HCl (5 mL x 2), dried (MgSO<sub>4</sub>) filtered and conc *in vacuo*. Purification was conducted via flash column chromatography.

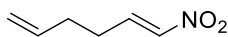
**General procedure D:** A solution of nitroalkane (5.00 mmol), triethylamine (0.35 mmol) and aldehyde (1.00 mmol) was stirred overnight under N<sub>2</sub> at rt. Nitroalkane and base removed in vacuo; purification by silica plug gave nitroalcohol which was used directly in the next step. Purified nitroalcohol (1.00 mmol) was dissolved in dry DCM (3 mL) under N<sub>2</sub> and cooled to - 78 °C. TFAA (1.20 mmol) was added dropwise and the reaction stirred for 5 min before dropwise addition of DIPEA (2.50 mmol). The reaction was stirred at - 78 °C until complete before warming to rt. The reaction was quenched with 2M HCl (15 mL) extracted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL x 3), washed with sat. NaCl solution (20 mL), dried (MgSO<sub>4</sub>) filtered and conc *in vacuo*. Purification was conducted via flash column chromatography.

**(E)-2-bromo-β-nitrostyrene (64b)**

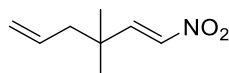


Prepared by *general procedure B* using 2-bromobenzaldehyde (5.01 g, 27.0 mmol) and nitromethane (3.70 mL, 68.6 mmol). Recrystallisation from Et<sub>2</sub>O and petrol afforded **64b** as long yellow needles (5.10 g, 22.4 mmol, 86 % yield) mp 83 – 85 °C (lit<sup>289</sup> 82 – 87 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.34 – 7.45 (2H, m, ArH) 7.56 (1H, d, *J* = 13.6, CHAr) 7.60 (1H, dd, *J* = 7.6, 2.0, ArH) 7.73 (1H, dd, *J* = 7.8, 1.7, ArH) 8.40 (1H, d, *J* = 13.6, CHNO<sub>2</sub>). NMR data is consistent with published data.<sup>289</sup>

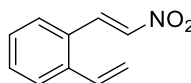
**(E)-1-nitro-hexa-1,5-diene (64c)**



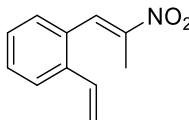
Prepared using *general procedure C* using 4-penten-1-al (1.00 g, 12.2 mmol) and nitromethane (3.40 mL, 61 mmol). Purification via flash column chromatography (5 % Et<sub>2</sub>O/hexanes) afforded **64c** as a colourless oil (1.02 g, 8.02 mmol, 66 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.27 – 2.41 (4H, m, CH<sub>2</sub>) 5.04 – 5.12 (2H, m, CH<sub>2</sub>) 5.78 (1H, ddt, *J* = 17.0, 10.4, 6.5, CH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>) 6.99 (1H, d, *J* = 13.4, 1.6, CHNO<sub>2</sub>) 7.26 (1H, dt, *J* = 13.4, 7.2, CHCHNO<sub>2</sub>); NMR data is consistent with published data.<sup>290</sup>

**(E)-1-nitro-2,2-dimethyl-hexa-1,5-diene (64q)**

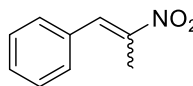
Prepared by *general procedure D* using 2,2-dimethylpent-4-enal (2.00 mL, 14.7 mmol) and nitromethane (4.00 mL, 74.1 mmol). Purification by flash column chromatography (2 % EtOAc/Hexanes) afforded **64q** as a colourless oil (1.19 g, 7.67 mmol, 52 %); IR  $\nu_{\text{max}}$  (thin film) 2966 (C-H) 1642 (C=C) 1524 (N-O, asym) 1348 (N-O, sym)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  1.13 (6H, s,  $\text{C}(\text{CH}_3)_2$ ) 2.18 (2H, apt dt,  $J = 7.4, 1.0$ ,  $\text{CCH}_2$ ) 5.07 (1H, dm,  $J = 17.0$ ,  $\text{CH}_2\text{CHCH}_2\text{-trans}$ ) 5.12 (1H, dm,  $J = 10.2$ ,  $\text{CH}_2\text{CHCH}_2\text{-cis}$ ) 5.70 (1H, ddt,  $J = 17.0, 10.3, 7.4$ ,  $\text{CH}_2\text{CH}$ ) 6.88 (1H, d,  $J = 13.6$ ,  $\text{CHCHNO}_2$ ) 7.25 (1H, d,  $J = 13.7$ ,  $\text{CHCHNO}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  26.1 (2C,  $\text{CH}_3$ ) 35.9 (q,  $\text{C}(\text{CH}_3)_2$ ) 46.3 ( $\text{C}(\text{CH}_3)_2\text{CH}_2$ ) 119.0 ( $\text{CCH}_2\text{CHCH}_2$ ) 133.1 ( $\text{CHCH}_2$ ) 138.0 ( $\text{CHNO}_2$ ) 150.9 ( $\text{CHCHNO}_2$ );  $m/z$  (ESI+) 194.1 (6 %,  $\text{M} + \text{K}^+$ ) 178.1 (72 %,  $\text{M} + \text{Na}^+$ ) 156.1 (100 %,  $\text{M} + \text{H}^+$ ); HRMS  $\text{C}_8\text{H}_{14}\text{NO}_2$  calcd. 156.1024 found 156.1030.

**(E)-2-vinyl- $\beta$ -nitrostyrene (64d)**

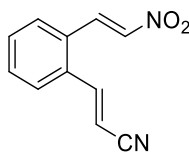
Prepared by *general procedure B* using 2-vinylbenzaldehyde **358d** (2.00 g, 15.1 mmol) and nitromethane (2.05 mL, 36.0 mmol). Purification by recrystallisation ( $\text{Et}_2\text{O}$ /Pet. Ether) afforded **64d** as a yellow oil (2.22 g, 12.7 mmol, 85 % yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  5.53 (1H, dd,  $J = 11.0, 0.7$ ,  $\text{ArCHCH}_2\text{-cis}$ ) 5.66 (1H, dd,  $J = 17.3, 0.8$ ,  $\text{ArCHCH}_2\text{-trans}$ ) 7.02 (1H, dd,  $J = 17.2, 11.0$ ,  $\text{ArCHCH}_2$ ) 7.34 (1H, t,  $J = 7.5$ ,  $\text{ArH}$ ) 7.47 (1H, t,  $J = 7.4$ ,  $\text{ArH}$ ) 7.50 (1H, d,  $J = 13.6$ ,  $\text{CHNO}_2$ ) 7.51 (1H, d,  $J = 7.9$ ,  $\text{ArH}$ ) 7.54 (1H, d,  $J = 7.9$ ,  $\text{ArH}$ ) 8.36 (1H, d,  $J = 13.5$ ,  $\text{CHCHNO}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  120.0 ( $\text{ArCHCH}_2$ ) 127.9 (q,  $\text{ArC}$ ) 127.9 (2C,  $\text{ArC}$ ) 128.4 ( $\text{ArC}$ ) 132.0 ( $\text{ArC}$ ) 133.7 ( $\text{ArCHCH}_2$ ) 137.1 ( $\text{CHCHNO}_2$ ) 138.3 ( $\text{CHNO}_2$ ) 139.7 (q,  $\text{ArC}$ );  $m/z$  ( $\text{CI}^+$ ) 176 (22 %,  $\text{M} + \text{H}^+$ ) 131 (100 %,  $\text{C}_{10}\text{H}_9\text{D}^+$ ); HRMS  $\text{C}_{10}\text{H}_{10}\text{NO}_2$  calcd. 176.0706 found 176.0707. NMR Data consistent with published data.<sup>241</sup>

**(E)-2-vinyl-β, β-methylnitrostyrene (499d)**

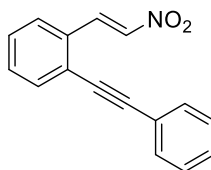
Prepared by *general procedure D* using 2-vinylbenzaldehyde **358d** (1.00 g, 7.57 mmol) and nitroethane (0.65 mL, 9.09 mmol). Purification by flash column chromatography (PhMe) afforded **499d** as a yellow oil (0.61 g, 3.22 mmol, 42 %); IR  $\nu_{\text{max}}$  (thin film) 1518 (N-O, asym) 1325 (N-O, sym)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  2.29 (3H, s,  $\text{CH}_3$ ) 5.42 (1H, apt d,  $J = 10.9$  Hz,  $\text{ArCHCH}_2\text{-cis}$ ) 5.69 (1H, apt d,  $J = 17.4$  Hz,  $\text{ArCHCH}_2\text{-trans}$ ) 6.80 (1H, dd,  $J = 17.3, 11.2$  Hz,  $\text{ArCHCH}_2$ ) 7.23 (1H, d,  $J = 7.9$ ,  $\text{ArH}$ ) 7.33 (1H, t,  $J = 7.4$ ,  $\text{ArH}$ ) 7.40 (1H, t,  $J = 7.4$ ,  $\text{ArH}$ ) 7.58 (1H, d,  $J = 7.8$ ,  $\text{ArH}$ ) 8.21 (1H, s,  $\text{ArCHCNO}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  14.2 ( $\text{CH}_3$ ) 118.2 ( $\text{CH}_2$ ) 126.6 ( $\text{ArC}$ ) 127.9 ( $\text{ArC}$ ) 129.2 ( $\text{ArC}$ ) 129.8 ( $\text{ArC}$ ) 130.7 (q,  $\text{ArCCHCNO}_2$ ) 132.8 ( $\text{CHCNO}_2$ ) 134.1 ( $\text{CHCH}_2$ ) 137.7 (q,  $\text{ArCCHCH}_2$ ) 148.8 (q,  $\text{CNO}_2$ );  $m/z$  ( $\text{CI}^+$ ) 190 (16 %,  $\text{M} + \text{H}^+$ ) 143 (56 %,  $\text{C}_{11}\text{H}_{11}^+$ ); HRMS  $\text{C}_{11}\text{H}_{12}\text{NO}_2$  ( $\text{M} + \text{H}^+$ ) calcd. 190.0868 found 190.0860.

**trans-β-Methyl-β-nitrostyrene (499a)**

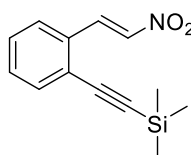
Prepared using *general procedure D*, using benzaldehyde **358a** (1.00 mL, 9.80 mmol) and nitroethane (3.50 mL, 48.9 mmol). Purification by flash column chromatography (100 % toluene) afforded **499a** as a yellow oil (0.75 g, 4.6 mmol, 47 % over 2 steps);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.46 (3H, s,  $\text{CH}_3$ ) 7.41 – 7.50 (5H, m,  $\text{ArH}$ ) 8.09 (1H, s,  $\text{ArCHC}(\text{CH}_3)\text{NO}_2$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  14.1 ( $\text{CH}_3$ ) 129.0 ( $\text{ArC}$ ) 130.0 (2C,  $\text{ArC}$ ) 130.0 (2C,  $\text{ArC}$ ) 132.5 (q,  $\text{ArC}$ ) 133.6 (q,  $\text{ArCCHCNO}_2$ ) 147.8 ( $\text{ArCCHC}(\text{CH}_3)\text{NO}_2$ ). NMR data is consistent with published data.<sup>291</sup>

**(*E,E*)-2-β-cyanovinyl-β-nitrostyrene (64h)**

To a solution of diethyl cyanomethylphosphonate (0.73 mL, 4.60 mmol) in dry THF (8 mL) under N<sub>2</sub> at -10 °C was added 1.15 M <sup>n</sup>BuLi in hexanes (4.0 mL, 4.60 mmol) and the reaction was stirred at -10 °C for 45 min. To the reaction at -10 °C was added 2-vinylbenzaldehyde (0.51 g, 3.85 mmol) in dry THF (3.5 mL) and the reaction was stirred to rt o/n. The reaction was quenched with brine (50 mL) extracted with Et<sub>2</sub>O (100 mL x 3), combined organic layers washed with brine (150 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to give the crude product. Purification via flash column chromatography (20 % EtOAc/Hexanes) afforded 3-(2-vinylphenyl)acrylonitrile as a mixture of (*E*)- and (*Z*)- isomers (85:15) (0.27 g, 1.74 mmol, 46 %) which was used *in situ*. A mixture isomers of 3-(2-vinylphenyl)acrylonitrile (0.27 g, 1.74 mmol), AgNO<sub>2</sub> (0.79 g, 5.1 mmol) 4 Å molecular sieves (0.54 g) and TEMPO (0.053 mg, 0.34 mmol) in DCE (6 mL) was stirred at 40 °C for 4 d under air. The reaction mixture was filtered through celite, washed with DCM and concentrated *in vacuo*. Purification by flash column chromatography (10-25 % EtOAc/Hexanes) afforded (*E*)-**64h** as the major isomer (142 mg, 0.71 mmol, 42 %) and (*Z*)-**64h** as the minor isomer (22 mg, 0.11 mmol, 6 %). mp<sub>(E)</sub> 93 – 95 °C; IR<sub>(E)</sub> ν<sub>max</sub> (thin film) 3107, 3051 (C-H) 2213 (C-N, nitrile) 1507 (C=C, Ar) 1340 (N-O symm) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ<sub>(E)</sub> 5.89 (1H, d, *J* = 16.3, CHCN) 7.48 (1H, d, *J* = 13.4, CHNO<sub>2</sub>) 7.51 – 7.60 (4H, m, ArH) 7.75 (1H, d, *J* = 16.3, CHCHCN) 8.27 (1H, d, *J* = 13.5, CHCHNO<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ<sub>(E)</sub> 101.5 (CHCN) 117.4 (q, CN) 127.7 (ArC) 128.6 (ArC) 129.3 (q, ArCCHCHNO<sub>2</sub>) 131.5 (ArC) 132.2 (ArC) 134.5 (q, ArCCHCHCN) 135.1 (CHCHNO<sub>2</sub>) 139.8 (CHNO<sub>2</sub>) 146.7 (CHCHCN); m/z<sub>(E)</sub> (EI) 200 (6 %, M<sup>+</sup>) 154 (100 %, C<sub>11</sub>H<sub>8</sub>N<sup>+</sup>) 127 (64 %, C<sub>9</sub>H<sub>5</sub>N<sup>+</sup>); HRMS<sub>(E)</sub> (C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>) calcd. 200.05858 found 200.058541. mp<sub>(Z)</sub> 111 – 115 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ<sub>(Z)</sub> 5.75 (1H, d, *J* = 11.8, CHCN) 7.47 (1H, d, *J* = 13.5, CHNO<sub>2</sub>) 7.51 (1H, d, *J* = 11.6, CHCHCN) 7.52 (1H, d, *J* = 7.0, ArH) 7.57 – 7.63 (2H, m, ArH) 7.90 (1H, d, *J* = 7.7, ArH) 8.16 (1H, d, *J* = 13.7, CHCHNO<sub>2</sub>); m/z<sub>(Z)</sub> (EI) 200 (4 %, M<sup>+</sup>) 154 (100 %, C<sub>11</sub>H<sub>8</sub>N<sup>+</sup>) 127 (48 %, C<sub>9</sub>H<sub>6</sub>N<sup>+</sup>); HRMS<sub>(Z)</sub> (C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>) calcd. 200.0586, found 200.0583.

**(E)-(2-phenylethynyl)- $\beta$ -nitrostyrene (64w)**

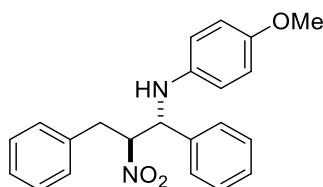
Prepared by *general procedure D* using aldehyde **358w** (6.86 g, 25.7 mmol). Purification by flash column chromatography (5 % EtOAc/Hexanes) afforded **64w** as an orange solid (4.79 g, 19.2 mmol, 66 % over two steps); mp 63 – 65 °C (lit 52 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  7.39 – 7.43 (4H, m, ArH) 7.48 (1H, t,  $J$  = 7.6, ArH) 7.59 – 7.63 (3H, m, ArH) 7.66 (1H, d,  $J$  = 7.7, ArH) 7.82 (1H, d,  $J$  = 13.7, ArCHCHNO<sub>2</sub>) 8.57 (1H, d, ArCHCHNO<sub>2</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  86.5 (ArCCPh) 97.1 (ArCCPh) 122.4 (q, ArC) 125.4 (q, ArCCPh) 127.9 (ArC) 128.7 (ArC) 128.9 (ArC) 129.3 (ArC) 131.3 (q, ArCCHCHNO<sub>2</sub>) 131.6 (ArC) 131.8 (ArC) 133.5 (ArC) 137.3 (CHCHNO<sub>2</sub>) 138.4 (CHNO<sub>2</sub>). NMR data consistent with published data.<sup>292</sup>

**(E)-trimethyl((2-(2-nitrovinyl)phenyl)ethynyl)silane (64v)**

Prepared by *general procedure D* using aldehyde **358v** (1.21 g, 5.98 mmol). Purification afforded **64v** as a pale yellow solid (0.92 g, 3.73 mmol, 62 %); mp 68 – 70 °C (lit<sup>293</sup> 68 – 70 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  0.32 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>) 7.39 (1H, td,  $J$  = 7.6, 1.3, ArH) 7.43 (1H, td,  $J$  = 7.6, 1.3, ArH) 7.55 (1H, apt d,  $J$  = 7.7, ArH) 7.58 (1H, dd,  $J$  = 7.8, 1.2, ArH) 7.83 (1H, d,  $J$  = 13.6, ArCHCHNO<sub>2</sub>) 8.45 (1H, d,  $J$  = 13.7, ArCHCHNO<sub>2</sub>);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  -0.15 (Si(CH<sub>3</sub>)<sub>3</sub>) 102.0 (q, ArCCCSi) 103.3 (q, ArCCCSi) 125.0 (q, ArCCCSi) 128.1 (ArC) 129.2 (ArC) 131.5 (ArC) 131.8 (q, ArCCHCHNO<sub>2</sub>) 133.7 (ArC) 137.3 (CHCHNO<sub>2</sub>) 138.5 (CHCHNO<sub>2</sub>). NMR data consistent with published data.<sup>293</sup>

### 3.3.5 Preparation of $\beta$ -nitroamines

#### 4-methoxy-*N*-((1*R*\*,2*S*\*)-2-nitro-1,3-diphenylpropyl)aniline (**357aa**)



To a solution of nitroalkene **64a** (0.23 g, 1.54 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at rt under  $\text{N}_2$  was added dropwise  $\text{LiHBEt}_3$  (1.0 M solution in THF, 1.60 mL, 1.60 mmol) and the reaction stirred for 25 min and a white ppt was formed. The reaction mixture was cooled to  $-78^\circ\text{C}$  and to this was added a solution of imine (0.34 g, 1.65 mmol) in  $\text{CH}_2\text{Cl}_2$  (4 mL). The reaction was stirred for 10 min before dropwise addition of trifluoroacetic acid (0.15 mL, 1.73 mmol) and the reaction was further stirred at  $-78^\circ\text{C}$  for 1 h. The reaction was warmed for 5 min then quenched with sat. aq.  $\text{NaHCO}_3$  solution (25 mL), extracted with  $\text{Et}_2\text{O}$  (15 mL x 3) washed with brine (20 mL), dried ( $\text{MgSO}_4$ ) filtered and concentrated *in vacuo* affording crude  $\beta$ -nitroamine **357aa** used without further purification (0.65 g, > 99% conversion);  $^1\text{H}$  NMR  $\delta$  3.23 (1H, dd,  $J = 14.8, 3.7$ ,  $\text{CH}_2$ ) 3.42 (1H, dd,  $J = 14.8, 10.5$ ,  $\text{CH}_2$ ) 3.71 (3H, s,  $\text{OCH}_3$ ) 4.23 (1H, *br s*,  $\text{NH}$ ) 4.89 (1H, *br d*,  $J = 5.4$ ,  $\text{CHN}$ ) 5.08 (1H, ddd,  $J = 10.5, 5.6, 3.7$ ,  $\text{CHNO}_2$ ) 6.55 (2H, dm,  $J = 8.9$ , PMP-*H*) 6.72 (2H, dm,  $J = 8.9$ , PMP-*H*) 7.10 (2H, m,  $\text{ArH}$ ) 7.21 – 7.39 (8H, m,  $\text{ArH}$ ). Data consistent with published data.<sup>62</sup>

### 3.3.6 Preparation and derivatisation of $\beta$ -nitro-(2,2,2)-trifluoroacetamides

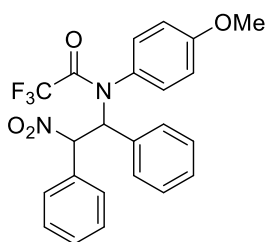
**General Procedure E:** To a solution of nitroalkane (1.00 mmol) in THF (5 mL) at  $-78^\circ\text{C}$  under  $\text{N}_2$  was added dropwise  $n\text{BuLi}$  (1.0 M solution in hexanes, 1.10 eq, 1.10 mmol). The reaction mixture was stirred for 15 min before addition of a solution of imine (1.13 mmol) in THF (3 mL). The reaction was stirred for 10 min before dropwise addition of trifluoroacetic acid (1.14 mmol) and the reaction was stirred at  $-78^\circ\text{C}$  for 1.5 h or until complete by TLC. The reaction was warmed for 5 min then quenched with sat. aq.  $\text{NaHCO}_3$  solution (15 mL), extracted with  $\text{Et}_2\text{O}$  (20 mL x 3) washed with brine (30 mL), dried ( $\text{MgSO}_4$ ) filtered and concentrated *in vacuo*. Crude  $\beta$ -nitroamine was re-dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and cooled to  $-78^\circ\text{C}$  under  $\text{N}_2$ . To this solution was added dropwise DIPEA (2.5 mmol) followed by dropwise addition of trifluoroacetic anhydride (2.5 mmol) and the reaction stirred for 18 h to rt. The reaction was quenched with 2 M  $\text{HCl}$



(20 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 3), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. to give the crude  $\beta$ -nitroacetamide. Purification was carried out via recrystallisation or flash column chromatography.

**General Procedure F:** To a solution of nitroalkene (1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at rt under N<sub>2</sub> was added dropwise LiHBEt<sub>3</sub> (1.0 M solution in THF, 1.05 eq, 1.05 mmol) and the reaction was stirred for 20 min and a white precipitate was formed. The reaction mixture was cooled to - 78 °C and to this was added a solution of imine (1.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL). The reaction was stirred for 10 min before dropwise addition of trifluoroacetic acid (1.14 mmol) and the reaction was stirred at - 78 °C for 1.5 h or until complete by TLC. The reaction was warmed for 5 min then quenched with sat. aq. NaHCO<sub>3</sub> solution (15 mL), extracted with Et<sub>2</sub>O (20 mL x 3) washed with brine (30 mL), dried (MgSO<sub>4</sub>) filtered and concentrated *in vacuo*. Crude  $\beta$ -nitroamine was re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and cooled to - 78 °C under N<sub>2</sub>. To this solution was added dropwise DIPEA (2.5 mmol) followed by dropwise addition of trifluoroacetic anhydride (2.5 mmol) and the reaction stirred for 18 h to rt. The reaction was quenched with 2 M HCl (20 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 3), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. to give the crude  $\beta$ -nitroacetamide. Purification was carried out via recrystallisation or flash column chromatography.

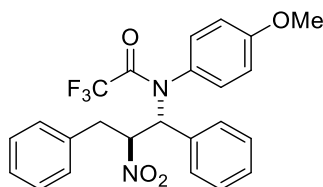
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(2-nitro-1,2-diphenylethyl)acetamide  
(352aa)**



Prepared by *general procedure E* using  $\alpha$ -nitrotoluene **4a** (1.00 g, 7.29 mmol) and imine **82a** (1.76 g, 8.28 mmol). Recrystallisation from benzene/hexanes afforded **352aa** as a white solid (1.36 g, 3.07 mmol, 42 %); mp 116 - 118 °C; IR  $\nu_{\max}$  (thin film) 1696 (C=O, amide) 1554 (N-O asymm) 1508 (C=C, Ar) 1358 (N-O symm) 1152 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{major}}$  3.83 (3H, s, OCH<sub>3</sub>) 6.33 (1H, *br s*, CHNO<sub>2</sub>) 6.42 (1H, *br s*, PMP-*H*) 6.73 (1H, dd, *J* = 8.9, 2.9, PMP-*H*) 6.76 (1H, *br s*, CHN) 6.94 (1H, dd, *J* = 8.9, 2.9, PMP-*H*) 7.00 (2H, d, *J* = 7.2, Ar*H*) 7.10 – 7.25 (7H, m, Ar*H*) 7.42 (2H, m, Ar*H*)

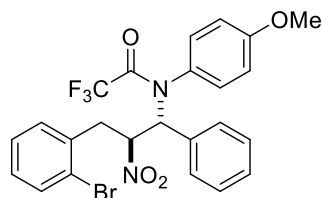
+ PMP-*H*);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta_{\text{major}}$  55.6 ( $\text{OCH}_3$ ) 64.3 ( $\text{CHN}$ ) 90.3 ( $\text{CHNO}_2$ ) 114.1 (PMP-*C*) 114.3 (PMP-*C*) 116.2 (q,  $J = 288.6$ ,  $\text{CF}_3$ ) 127.4 (q, ArC) 128.7 (ArC) 128.8 (2C, ArC) 129.2 (2C, ArC) 129.2 (2C, ArC) 129.8 (2C, ArC) 130.4 (PMP-*C*) 131.3 (ArC) 132.4 (PMP-*C*) 133.1 (q, ArC) 158.0 (q,  $J = 36.1$ ,  $\text{COCF}_3$ ) 160.5 (q, ArCO) further signals indistinguishable;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta - 67.4$  ppm (3F, s,  $\text{CF}_3$ );  $m/z$  ( $\text{CI}^+$ ) 444 (13 %,  $\text{M} + \text{H}^+$ ) 398 (100 %,  $\text{C}_{23}\text{H}_{19}\text{F}_3\text{NO}_2^+$ ) 308 (8 %,  $\text{C}_{16}\text{H}_{13}\text{F}_3\text{NO}_2^+$ ) 218 (9 %,  $\text{C}_9\text{H}_7\text{F}_3\text{NO}_2^+$ ); HRMS ( $\text{C}_{23}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_4$ ) calcd. 445.13752, found 445.137189; Anal. Calcd. For  $\text{C}_{23}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$ : C, 62.16; H, 4.31; N, 6.30; found: C, 62.41; H, 4.29; N, 6.18 %.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-1,3-diphenylpropyl)acetamide (102aa)**



Prepared by *general procedure F* using trans- $\beta$ -nitrostyrene **64a** (1.50 g, 10.1 mmol) and imine **82a** (2.33 g, 11.0 mmol). Purification by recrystallisation (MeOH/hexanes) afforded **102aa** as colourless crystals (3.00 g, 6.56 mmol, 66 %) mp 136-138 °C (lit<sup>62</sup> 128-131 °C);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  3.47 (1H, dd,  $J = 14.2$ , 11.2,  $\text{CH}_2\text{Ph}$ ) 3.56 (1H, dd,  $J = 14.8$ , 3.2,  $\text{CH}_2\text{Ph}$ ) 3.83 (3H, s,  $\text{OCH}_3$ ) 5.61 (1H, apt t,  $J = 10.5$ ,  $\text{CHNO}_2$ ) 6.04 (1H, br s,  $\text{CHN}$ ) 6.40 (1H, br s, ArH) 6.72 (1H, dd,  $J = 8.5$ , 3.0, ArH) 6.92 (1H, dd,  $J = 8.8$ , 3.1, ArH) 7.04 (1H, d,  $J = 8.4$ , ArH) 7.12 (2H, d,  $J = 7.3$ , ArH) 7.22-7.27 (3H, m, ArH) 7.28-7.38 (5H, m). NMR Data is consistent with published data.<sup>62</sup>

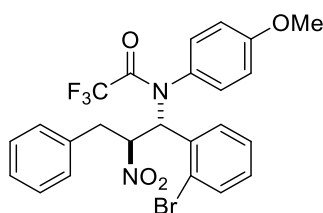
***N*-((1*R*\*,2*S*\*)-3-(2-bromophenyl)-2-nitro-1-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (102ba)**



Prepared by *general procedure F* using nitroalkene **64b** (2.29 g, 10.0 mmol) and imine **82a** (2.32 g, 11.0 mmol). Purification by recrystallisation (MeOH/Hexanes) afforded

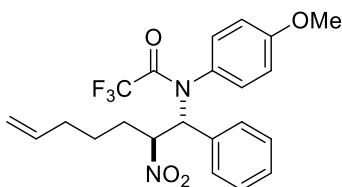
**102ba** as colourless crystals (3.33 g, 6.18 mmol, 62 %) mp 118 – 120 °C (lit<sup>201</sup> 118 – 120 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.60 (1H, dd, *J* = 14.4, 11.5, CH<sub>2</sub>Ar) 3.78 (1H, dd, *J* = 14.3, 3.8, CH<sub>2</sub>Ar) 3.81 (3H, s, OMe) 5.75 (1H, td, *J* = 11.6, 3.5, CHNO<sub>2</sub>) 6.28 (2H, m, CHN & PMP-*H*) 6.62 (1H, dd, *J* = 8.9, 2.9, PMP-*H*) 6.91 (1H, dd, *J* = 8.8, 2.8, PMP-*H*) 7.07 (2H, d, *J* = 7.4, CH) 7.15 – 7.32 (6H, m, ArH) 7.40 (1H, d, *J* = 7.1, ArH) 7.60 (1H, m, ArH). NMR data consistent with published data.<sup>65</sup>

***N*-((1*R*\*,2*S*\*)-1-(2-bromophenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (102ab)**



Prepared by *general procedure F* using *trans*-β-nitrostyrene **64a** (0.60 g, 4.02 mmol) and imine **82b** (1.29 g, 4.44 mmol). Purification by flash chromatography (40 % DCM/Hexane, followed by second column 10 % Et<sub>2</sub>O/Hexane) afforded **102ab** as a white solid (0.50 g, 0.93 mmol, 24 %) mp 169 - 172 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.57 (2H, m, CH<sub>2</sub>) 3.80 (3H, s, OMe) 5.49 (1H, td, *J* = 10.9, 3.6, CHNO<sub>2</sub>) 6.28 (1H, d, *J* = 8.0, ArH) 6.58 (1H, dd, *J* = 9.0, 3.0, ArH) 6.79 (1H, d, *J* = 11.0, CHN) 6.84 (1H, d, *J* = 7.5, ArH) 6.91 (1H, dd, *J* = 8.5, 3.0, ArH) 7.01 – 7.05 (2H, m, ArH) 7.15 (1H, td, *J* = 7.6, 1.6, ArH) 7.25 (2H, d, *J* = 8.5, ArH) 7.32 – 7.39 (3H, m, ArH) 7.62 (1H, dd, *J* = 8.0, 1.0, ArH); NMR data is consistent with published data.<sup>63</sup>

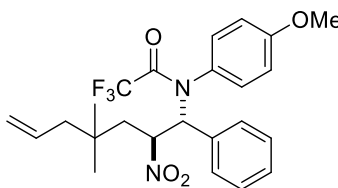
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-1-phenylhept-6-en-1-yl)acetamide (102ca)**



Prepared by *general procedure F* using nitroalkene **64c** (1.02 g, 8.02 mmol) and imine **82a** (1.91 g, 9.06 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/hexanes) afforded **102ca** as a mixture of diastereoisomers (>90:10) as a yellow oil (1.97 g, 4.52 mmol, 56 %); IR ν<sub>max</sub> (CDCl<sub>3</sub> cast) 2936 (C-H) 1697 (C=O) 1608 (Ar, C=C)

1585 (Ar, C=C) 1554 (N-O) 1510 (Ar, C=C) 1254 (C-O) 1180 (CF<sub>3</sub>, C-F) 1033 (C-N) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.54 – 1.63 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) 2.16 – 2.34 (4H, m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) 3.86 (3H, s, OCH<sub>3</sub>) 5.08 (1H, dm, *J* = 10.1, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>-cis) 5.12 (1H, dm, *J* = 17.1, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>-trans) 5.33 (1H, apt br t, *J* = 10.0, CHNO<sub>2</sub>) 5.78 – 5.88 (1H, ddt, *J* = 17.1, 10.2, 6.7, CH<sub>2</sub>CHCH<sub>2</sub>) 6.04 (1H, br m, CHN) 6.29 (1H, br d, *J* = 7.2, ArH) 6.68 (1H, dd, *J* = 8.9, 6.6, PMP-*H*) 6.90 (1H, dd, *J* = 8.7, 2.8, PMP-*H*) 6.96 (1H, br d, *J* = 1.9, PMP-*H*) 7.09 (2H, d, *J* = 7.4, ArH) 7.25 – 7.36 (3H, dm, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 24.9 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) 31.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) 32.6 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 59.3 (CHN) 87.8 (CNO<sub>2</sub>) 114.0 (ArC) 114.3 (ArC) 116.1 (CH<sub>2</sub>CHCH<sub>2</sub>R) 116.3 (q, *J* = 286.9, CF<sub>3</sub>) 128.8 (2C, ArC) 129.1 (q) 129.2 (2C, ArC) 129.7 (ArC) 130.1 (ArC) 132.2 (ArC) 133.4 (q) 137.2 (CH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>) 158.0 (q, *J* = 35.3, COCF<sub>3</sub>) 160.5 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz) δ -67.7 (3F, s, CF<sub>3</sub>); *m/z* (CI<sup>+</sup>) 437 (44 %, *M* + H<sup>+</sup>) 390 (100 %, C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 308 (17 %, C<sub>16</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub>) 220 (16 %, C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub>); HRMS (C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 437.1688, found 437.1682.

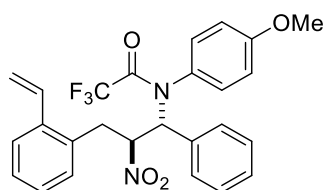
***N*-((1*R*\*,2*S*\*)-4,4-dimethyl-2-nitro-1-phenylhept-6-en-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**102qa**)**



Prepared by *general procedure F* using nitroalkene **64q** (0.70 g, 4.51 mmol) and imine **82a** (1.08 g, 5.11 mmol). Purification by flash column chromatography (50 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) afforded **102qa** as a yellow oil (1.41g, 3.04 mmol, 67 %); IR ν<sub>max</sub> (thin film) 2964 (C-H) 1701 (C=O, amide) 1556 (N-O asym) 1510 (C=C, Ar) 1350 (N-O, sym) 1181, 1157 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 0.95 (3H, s, CH<sub>3</sub>) 1.07 (3H, s, CH<sub>3</sub>) 2.05 – 2.11 (3H, m, CH<sub>2</sub>) 2.33 (1H, dd, *J* = 15.3, 11.2, CH<sub>2</sub>CHNO<sub>2</sub>) 3.81 (3H, s, OCH<sub>3</sub>) 5.11 (1H, dm, *J* = 17.0, CH<sub>2</sub>CHCH<sub>2</sub>-trans) 5.16 (1H, dm, *J* = 10.3, CH<sub>2</sub>CHCH<sub>2</sub>-cis) 5.53 – 5.78 (2H, m, CHNO<sub>2</sub> & CHN) 5.84 (1H, ddt, *J* = 17.1, 10.1, 7.4, CH<sub>2</sub>CHCH<sub>2</sub>) 6.40 (1H, m, PMP-*H*) 6.71 (1H, dd, *J* = 8.8, 2.2, PMP-*H*) 6.86 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 6.93 (1H, apt d, *J* = 8.1, PMP-*H*) 7.12 (2H, d, *J* = 7.4, ArH) 7.25 (2H, apt t, *J* = 7.7, ArH) 7.32 (1H, tm, *J* = 7.4, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 25.5 (CH<sub>3</sub>) 26.6 (CH<sub>3</sub>) 33.4 (C(CH<sub>3</sub>)<sub>2</sub>) 42.1 (CH<sub>2</sub>CHNO<sub>2</sub>) 47.9 (CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>) 55.6 (OCH<sub>3</sub>)

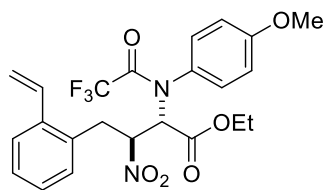
66.8 (CHN) 85.0 (CHNO<sub>2</sub>) 113.9 (PMP-C) 114.5 (PMP-C) 116.3 (q,  $J = 289.4$ , CF<sub>3</sub>) 118.8 (CH<sub>2</sub>CHCH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>) 128.5 (q, ArCN) 128.8 (2C, ArC) 129.7 (2C, ArC) 129.8 (ArC) 130.3 (PMP-C) 131.9 (PMP-C) 132.9 (q, ArCCHN) 134.2 (CH<sub>2</sub>CHCH<sub>2</sub>) 157.9 (q,  $J = 34.8$ , COCF<sub>3</sub>) 160.4 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.4 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) m/z 503 (21 %, M + K<sup>+</sup>) 497 (40 %, M + CH<sub>3</sub>OH + H<sup>+</sup>) 465 (100 %, M + H<sup>+</sup>); HRMS (C<sub>24</sub>H<sub>28</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 465.2001, found 465.2018.

**2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1*R*\*,2*S*\*)-2-nitro-1-phenyl-3-(2-vinylphenyl)propyl)acetamide (102da)**



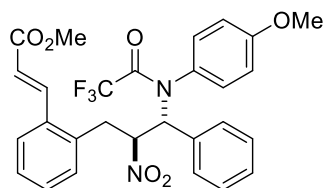
Prepared by *general procedure F* using nitrostyrene **64d** (1.22 g, 6.98 mmol) and imine **82a** (1.63 g, 7.72 mmol). Purification via flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes followed by 20 % Et<sub>2</sub>O/Hexanes) afforded **102da** as a white solid (1.27 g, 2.62 mmol, 38 %); mp 90 – 92 °C; IR  $\nu_{\text{max}}$  (thin film) 1696 (C=O stretch, amide) 1556 (N-O, asym) 1510 (C=C, Ar) 1300 (N-O sym) 1153 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.56 (1H, dd,  $J = 14.5$ , 11.2, ArCH<sub>2</sub>) 3.67 (1H, dd,  $J = 11.2$ , 3.3, ArCH<sub>2</sub>) 3.81 (3H, s, OCH<sub>3</sub>) 5.50 (1H, dd,  $J = 10.9$ , 1.1, ArCHCH<sub>2-trans</sub>) 5.74 (1H, dd,  $J = 17.4$ , 1.1, ArCHCH<sub>2-cis</sub>) 5.74 (1H, br s, CHNO<sub>2</sub>) 5.95 (1H, br s, CH) 6.52 (1H, br s, CH) 6.74 (1H, br d,  $J = 8.8$ , PMP-H) 6.89 (1H, dd,  $J = 8.8$ , 2.8, PMP-H) 7.03 (1H, br d,  $J = 8.1$ , PMP-H) 7.07 (1H, dd,  $J = 17.4$ , 10.9, ArCHCH<sub>2</sub>) 7.15 (3H, br d,  $J = 7.4$ , ArH) 7.23 – 7.27 (3H, m, ArH) 7.29 (1H, dd,  $J = 7.7$ , 1.1, ArH) 7.32 (1H, d,  $J = 7.5$ , ArH) 7.52 (1H, d,  $J = 7.5$ , ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  35.6 (ArCH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 66.9 (CHN) 88.9 (CHNO<sub>2</sub>) 114.0 (PMP-C) 114.7 (PMP-C) 116.3 (q,  $J = 291.2$ , CF<sub>3</sub>) 118.0 (ArCHCH<sub>2</sub>) 127.0 (ArC) 128.4 (ArC) 128.5 (ArC) 128.8 (q, ArC) 129.0 (2C, ArC) 129.5 (ArC) 129.8 (ArC) 129.9 (ArC) 130.4 (PMP-C) 131.7 (PMP-C) 131.8 (q, ArCCHCH<sub>2</sub>) 133.3 (q, ArC) 134.2 (ArCCHCH<sub>2</sub>) 137.6 (q, ArC) 158.2 (q,  $J = 36.0$ , COCF<sub>3</sub>) 160.5 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.3 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 485 (100 %, M + H<sup>+</sup>) 438 (63 %, C<sub>26</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>2</sub>) 308 (55 %, C<sub>16</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub>) 219 (94 %, C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>NO<sub>2</sub>); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 485.1683, found 485.1682.

**ethyl (2*S*\*,3*S*\*)-3-nitro-2-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)-4-(2-vinylphenyl)butanoate (102df)**



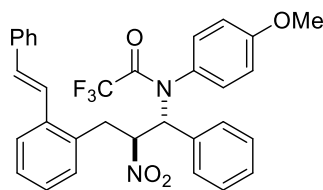
Prepared by *general procedure F* using 2-vinyl-*trans*- $\beta$ -nitrostyrene **64d** (0.78g, 4.42 mmol) and Ethyl *N*-(4-methoxyphenyl)-formimidate **82f** (1.04 g, 5.02 mmol). Purification via flash column chromatography afforded the product **102df** as a white solid (1.34 g, 2.79 mmol, 63 %) mp 105 - 106 °C; IR  $\nu_{\text{max}}$  (thin film) 2983 (C-H) 1747 (C=O, ester) 1701 (C=O, amide) 1561 (N-O, asym) 1510 (C=C, Ar) 1300 (N-O, sym) 1157 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.30 (3H, t, *J* = 7.1, CH<sub>2</sub>CH<sub>3</sub>) 3.15 (1H, dd, *J* = 14.1, 11.7, ArCH<sub>2</sub>) 3.51 (1H, dd, *J* = 14.1, 3.6, ArCH<sub>2</sub>) 3.87 (3H, s, ArOCH<sub>3</sub>) 4.30 (2H, q, *J* = 7.1, CH<sub>2</sub>CH<sub>3</sub>) 4.94 (1H, d, *J* = 8.5, CHN) 5.43 (1H, d, *J* = 10.9, ArCHCH<sub>2</sub>-*cis*) 5.61 (1H, ddd, *J* = 11.7, 8.8, 3.6, CHNO<sub>2</sub>) 5.72 (1H, d, *J* = 17.1, ArCHCH<sub>2</sub>-*trans*) 6.84 (1H, dd, *J* = 17.1, 11.0, ArCHCH<sub>2</sub>) 6.97 (2H, *br s*, PMP-*H*) 7.01 (1H, d, *J* = 7.6, Ar*H*) 7.22 (1H, t, *J* = 7.5, Ar*H*) 7.30 (1H, t, *J* = 7.6, Ar*H*) 7.30 (1H, *br s*, PMP-*H*) 7.53 (2H, m, Ar*H*, PMP-*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  13.9 (CH<sub>2</sub>CH<sub>3</sub>) 35.5 (ArCH<sub>2</sub>) 55.7 (ArOCH<sub>3</sub>) 63.3 (OCH<sub>2</sub>CH<sub>3</sub>) 67.5 (CHN) 86.9 (CNO<sub>2</sub>) 114.7 (PMP-*C*) 115.3 (PMP-*C*) 116.0 (q, CF<sub>3</sub>) 118.2 (ArCHCH<sub>2</sub>) 126.8 (Ar*C*) 128.4 (Ar*C*) 128.6 (Ar*C*) 129.2 (PMP-*C*) 129.6 (PMP-*C*) 130.1 (Ar*C*) 131.1 (q, ArCCH<sub>2</sub>CHNO<sub>2</sub>) 132.3 (q, ArCN) 133.3 (CHCH<sub>2</sub>) 137.4 (q, ArCCHCH<sub>2</sub>) 158.6 (q, *J* = 37.1, COCF<sub>3</sub>) 160.6 (q, ArCOCH<sub>3</sub>) 166.5 (q, COCH<sub>2</sub>CH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.9 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 544 (58 %, M + MeCN + Na<sup>+</sup>) 481 (100 %, M + H<sup>+</sup>) 434 (9 %, C<sub>23</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>4</sub>); HRMS (C<sub>23</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>) calcd. 481.1616, found 481.1586.

**methyl (*E*)-3-(2-((2*S*\*,3*R*\*)-2-nitro-3-phenyl-3-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)propyl)phenyl)acrylate (**102ea**)**



To a solution of  $\beta$ -nitroacetamide **102da** (209 mg, 0.43 mmol) in degassed methyl acrylate (4.40 mL, 48.6 mmol) was added Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst (29.4 mg, 0.046 mmol) and the reaction was stirred at 75 °C o/n. Purification by flash column chromatography using EtOAc/Hexanes (10-20 %) followed by a second column using EtOAc/Hexanes (40 %) afforded **102ea** as a colourless oil (170 mg, 0.34 mmol, 82 %); mp 67 - 70 °C; IR  $\nu_{\text{max}}$  (thin film) 2949, 2838 (C-H) 1695 (C=O, amide & ester) 1633 (C=C) 1555 (N-O, asym) 1508 (C=C, Ar) 1317 (N-O, sym) 1153 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.63 (1H, dd,  $J$  = 14.7, 11.6, ArCH<sub>2</sub>) 3.73 (1H, dd,  $J$  = 14.6, 3.6, ArCH<sub>2</sub>) 3.81 (3H, s, ArOCH<sub>3</sub>) 3.86 (3H, s, COOCH<sub>3</sub>) 5.57 (1H, *br s*, CHNO<sub>2</sub>) 6.15 (1H, *br s*, CHN) 6.36 (1H, *br s*, ArH) 6.48 (1H, d,  $J$  = 15.7, ArCHCHCO<sub>2</sub>CH<sub>3</sub>) 6.66 (1H, *apt d*,  $J$  = 7.3, ArH) 6.99 (1H, dd,  $J$  = 8.7, 2.5, ArH) 7.07 (2H, d,  $J$  = 7.2, ArH) 7.16 – 7.37 (7H, m, ArH) 7.60 (1H, dd,  $J$  = 7.6, 2.2, ArH) 8.08 (1H, d,  $J$  = 15.7, ArCHCHCO<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  35.5 (ArCH<sub>2</sub>) 52.0 (COOCH<sub>3</sub>) 55.6 (ArOCH<sub>3</sub>) 65.9 (CHN) 89.2 (CNO<sub>2</sub>) 114.4 (PMP-C) 114.5 (PMP-C) 116.3 (q,  $J$  = 287.3, CF<sub>3</sub>) 121.4 (CHCOOCH<sub>3</sub>) 127.4 (ArC) 128.1 (ArC) 128.7 (ArC) 128.9 (ArC) 129.5 (ArC) 129.8 (ArC) 130.6 (ArC) 130.8 (2C, PMP-C) 132.1 (q, ArCCHCHCO) 133.0 (q, ArCCH<sub>2</sub>) 133.7 (q, ArCN) 133.7 (ArCCN) 140.9 (CHCHCOOCH<sub>3</sub>) 158.4 (q,  $J$  = 35.4, COCF<sub>3</sub>) 160.5 (ArCOCH<sub>3</sub>) 167.0 (q, COOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.1 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 543 (22 %, M + H<sup>+</sup>) 511 (100 %, C<sub>27</sub>H<sub>22</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub><sup>+</sup>) 220 (60 %, C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub>D<sup>+</sup>); HRMS (C<sub>28</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>) calcd. 543.1743, found 543.1740.

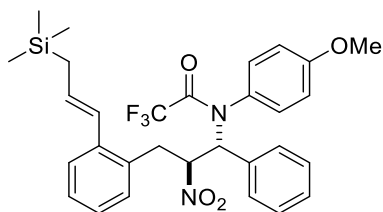
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-1-phenyl-3-(2-((*E*)-styryl)phenyl)propyl)acetamide (102ga)**



To a degassed mixture of nitroacetamide **102da** (876 mg, 1.81 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst (56.7 mg, 0.091 mmol) followed by degassed styrene (2.10 mL, 18.9 mmol) and the reaction was heated to 40 °C for 7 h before the addition of a second portion of catalyst (28.6 mg, 0.05 mmol) and degassed styrene (1.00 mL, 9.00 mmol), the reaction was heated o/n until complete by TLC. The reaction was concentrated *in vacuo*. Purification by flash column chromatography using EtOAc/Hexanes (0-10 %) afforded **102ga** as a white solid (0.79 g, 1.41 mmol, 78 %); mp 68 - 70 °C; IR  $\nu_{\text{max}}$  (thin film) 1697 (C=O, amide) 1557 (N-O, asymm) 1510 (C=C, Ar) 1301 (N-O, symm) 1182 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.56 (1H, dd, *J* = 14.4, 11.5, CH<sub>2</sub>) 3.70 (3H, s, OCH<sub>3</sub>) 3.77 (1H, dd, *J* = 14.4, 3.3, CH<sub>2</sub>) 5.65 (1H, br s, CHNO<sub>2</sub>) 6.02 (1H, br s, CHN) 6.22 (1H, br s, PMP-*H*) 6.39 (1H, br s, PMP-*H*) 6.62 (1H, br d, *J* = 7.3, PMP-*H*) 6.89 (1H, dd, *J* = 8.5, 1.8, PMP-*H*) 7.05 (2H, br d, *J* = 6.5, Ar*H*) 7.12 (1H, d, *J* = 7.5, 1.2, Ar*H*) 7.13 (1H, d, *J* = 16.0, PhCHCHAr) 7.19 (2H, t, *J* = 7.8, Ar*H*) 7.24 (1H, td, *J* = 7.5, 1.2, Ar*H*) 7.28 (1H, m, Ar*H*) 7.33 (2H, m, Ar*H*) 7.42 (2H, m, Ar*H*) 7.48 (1H, d, *J* = 16.0, ArCHCHPh) 7.64 (1H, d, *J* = 7.6, Ar*H*) 7.67 (2H, d, *J* = 7.4, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.1 (CH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 66.3 (CHN) 89.3 (CHNO<sub>2</sub>) 113.5 (PMP-C) 114.9 (PMP-C) 116.3 (q, CF<sub>3</sub>, *J* = 290.3) 125.3 (ArCHCHPh) 127.1 (ArC) 127.2 (2C, ArC) 128.3 (ArC) 128.5 (ArC) 128.6 (2C, ArC) 128.9 (2C, ArC) 129.0 (2C, ArC) 129.4 (2C, ArC) 129.7 (ArC) 130.4 (2C, PMP-C) 131.7 (q, ArCCHCHPh) 132.2 (q, ArCN) 132.8 (ArCHCHPh) 133.2 (q, ArCCHN) 136.8 (q, ArCCH<sub>2</sub>) 137.1 (q, ArCCHCHArCH<sub>2</sub>) 158.3 (q, *J* = 35.6, COCF<sub>3</sub>) 160.3 (ArCOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.2 ppm (3F, s, CF<sub>3</sub>); *m/z* (CI<sup>+</sup>) 578 (20 %, M + H<sub>2</sub>O + H<sup>+</sup>) 560 (7 %, M + H<sup>+</sup>) 514 (14 %, C<sub>32</sub>H<sub>27</sub>F<sub>3</sub>NO<sub>2</sub>); HRMS (C<sub>32</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>F<sub>3</sub>) calcd. 560.1923, found 560.1919.

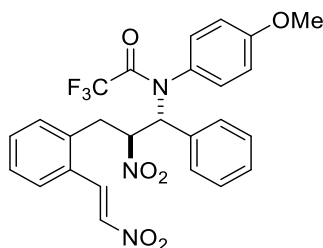


**2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1*R*\*,2*S*\*)-2-nitro-1-phenyl-3-(2-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)phenyl)propyl)acetamide (**102ia**)**



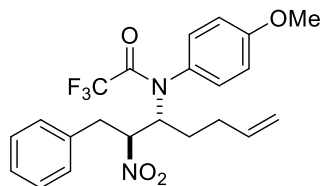
To a solution of nitroacetamide **102da** (149 mg, 0.31 mmol) in degassed CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added Hoveyda-Grubbs 2<sup>nd</sup> generation catalyst (10.3 mg, 16 μmol), followed by dropwise addition of allyltrimethylsilane (100 μL, 0.62 mmol), and the reaction was stirred at reflux o/n before the addition of a second portion of addition of allyltrimethylsilane (100 μL, 0.62 mmol). The reaction was stirred for a further 4 h and concentrated *in vacuo*. Purification by flash column chromatography using EtOAc/Hexanes (0 - 10 % EtOAc/Hexanes) afforded **102ia** as a mixture of isomers (90:10) as a colourless oil (68.0 mg, 0.12 mmol, 39 %); IR  $\nu_{\text{max}}$  (thin film) 2952, 2845 (C-H) 1696 (C=O, amide) 1555 (N-O, asymm) 1508 (C=C, Ar) 1299 (N-O, symm) 1152 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  0.13 (9H, s, Si((CH<sub>3</sub>)<sub>3</sub>)) 1.85 (2H, dm,  $J$  = 8.5, CH<sub>2</sub>Si) 3.52 (1H, dd,  $J$  = 14.4, 11.2, ArCH<sub>2</sub>) 3.71 (1H, dd,  $J$  = 14.4, 3.2, ArCH<sub>2</sub>) 3.82 (3H, s, OCH<sub>3</sub>) 5.67 – 6.04 (2H, m, CHNO<sub>2</sub> & CH) 6.27 (1H, dt,  $J$  = 15.2, 8.3, CHCH<sub>2</sub>Si) 6.56 (1H, br s, CH) 6.57 (1H, d,  $J$  = 15.3, CHCHCH<sub>2</sub>Si) 6.76 (1H, apt d,  $J$  = 8.0, PMP-*H*) 6.89 (1H, dd,  $J$  = 8.7, 2.9, PMP-*H*) 7.04 (1H, br d,  $J$  = 8.0, PMP-*H*) 7.10 – 7.34 (8H, m, ArH) 7.46 (1H, d,  $J$  = 7.8, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  -1.65 (Si(CH<sub>3</sub>)<sub>3</sub>) 24.7 (CH<sub>2</sub>Si(CH<sub>3</sub>)<sub>3</sub>) 35.9 (ArCH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 67.1 (CHN) 88.6 (CHNO<sub>2</sub>) 114.2 (PMP-C) 114.5 (PMP-C) 116.3 (q,  $J$  = 288.5, CF<sub>3</sub>) 124.9 (CHCHCH<sub>2</sub>Si) 126.6 (ArC) 127.2 (CH) 128.3 (ArC) 128.9 (3C, ArC) 129.5 (2C, ArC) 129.8 (CH) 130.0 (CH) 130.4 (CH) 130.8 (q, ArCCH<sub>2</sub>) 131.7 (q, ArCN) 132.0 (CHCHCH<sub>2</sub>Si) 133.5 (q, ArCCHN) 137.9 (q, ArCCHCHCH<sub>2</sub>Si) 158.2 (q, COCF<sub>3</sub>) 160.5 (ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  -67.2 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 588 (100 %, M + NH<sub>4</sub><sup>+</sup>); HRMS (EI) (C<sub>30</sub>H<sub>33</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>Si) calcd. 570.2156, found 570.2156.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-3-(2-((*E*)-2-nitrovinyl)phenyl)-1-phenylpropyl)acetamide (102ka)**



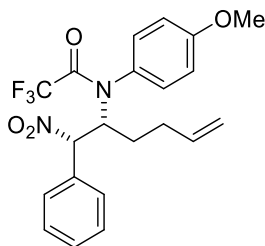
A mixture of alkene **102da** (0.30 g, 0.62 mmol), AgNO<sub>2</sub> (0.29 g, 1.86 mmol) 4 Å molecular sieves (0.19 g) and TEMPO (0.02 mg, 0.12 mmol) in DCE (6 mL) was stirred at 70 °C for 1.5 h under air. On completion, the reaction mixture was filtered through celite, washed with DCM and concentrated *in vacuo*. Purification via flash column chromatography (10-20 % EtOAc/Hexanes) afforded **102ka** as a white solid (271 mg, 0.51 mmol, 83 %) as a mixture of isomers (90:10); mp 72 – 74 °C; IR  $\nu_{\text{max}}$  (thin film) 2968, 2841 (C-H) 1695 (C=O, amide) 1556 (N-O, asym) 1509 (C=C, Ar) 1341 (N-O, sym) 1180, 1154 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{anti}}$  3.68 (1H, dd, *J* = 14.7, 10.9, CH<sub>2</sub>) 3.72 (1H, dd, *J* = 14.7, 4.6, CH<sub>2</sub>) 3.83 (3H, s, OCH<sub>3</sub>) 5.70 (1H, *br s*, CHNO<sub>2</sub>) 5.99 (1H, *br s*, CHN) 6.50 (1H, *br s*, PMP-*H*) 6.74 (1H, dd, *J* = 8.7, 2.4, PMP-*H*) 6.98 (1H, dd, *J* = 8.7, 2.7, PMP-*H*) 7.09 (1H, d, *J* = 7.6, PMP-*H*) 7.13 (2H, m, Ar*H*) 7.25 (2H, d, *J* = 7.5, Ar*H*) 7.30 – 7.42 (4H, m, Ar*H*) 7.55 (1H, d, *J* = 13.4, CHNO<sub>2</sub>) 7.56 (1H, dd, *J* = 7.7, 1.1, Ar*H*) 8.37 (1H, d, *J* = 13.4, CHCHNO<sub>2</sub>)  $\delta_{\text{syn}}$  3.02 (1H, dd, *J* = 15.2, 2.9, CH<sub>2</sub>) 3.18 (1H, dd, *J* = 15.2, 11.6, CH<sub>2</sub>) 7.93 (1H, d, *J* = 13.4, CHCHNO<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta_{\text{anti}}$  35.3 (CH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 66.8 (CHN) 89.6 (CHNO<sub>2</sub>) 114.2 (PMP-C) 115.0 (PMP-C) 116.3 (q, *J* = 289.1, CF<sub>3</sub>) 128.0 (ArC) 128.5 (q, ArC) 129.0 (3C, ArC) 129.3 (q, ArC) 129.4 (2C, ArC) 130.0 (CH) 130.2 (CH) 131.4 (PMP-C) 131.7 (*br CH*) 132.5 (ArC) 133.0 (q, ArC) 135.2 (CHCHNO<sub>2</sub>) 135.3 (q, ArC) 139.4 (CHCHNO<sub>2</sub>) 158.5 (q, *J* = 36.0, COCF<sub>3</sub>) 160.6 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta_{\text{anti}}$  – 67.4 ppm (3F, s, CF<sub>3</sub>)  $\delta_{\text{syn}}$  – 67.2 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 552 (23 %, M + Na<sup>+</sup>) 547 (45 %, M + NH<sub>4</sub><sup>+</sup>) 530 (100%, M + H<sup>+</sup>); HRMS (C<sub>26</sub>H<sub>23</sub>F<sub>3</sub>N<sub>3</sub>O<sub>6</sub>) calcd. 530.1539, found 530.1535.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((2*S*\*,3*R*\*)-2-nitro-1-phenylhept-6-en-3-yl)acetamide (102ac)**



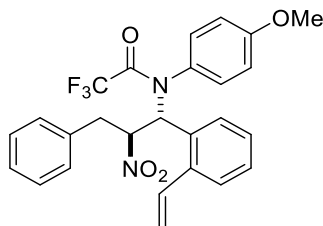
Prepared by *general procedure F* using trans- $\beta$ -nitrostyrene **64a** (0.53 g, 3.60 mmol) and imine **82c** (0.77 g, 4.07 mmol). Purification by flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) and recrystallisation (Et<sub>2</sub>O/Hexanes) afforded **102ac** as colourless crystals (0.72 g, 1.65 mmol, 46 %); mp 86 - 88 °C; IR  $\nu_{\text{max}}$  (thin film) 2935 (C-H) 1697 (C=O, amide) 1554 (N-O asym) 1509 (C=C, Ar) 1298 (N-O sym) 1151 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.56 (1H, m, CHNCH<sub>2</sub>) 1.80 (1H, apt br d,  $J$  = 8.3, CHNCH<sub>2</sub>) 2.16 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CH) 2.26 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CH) 3.34 (1H, dd,  $J$  = 14.8, 3.8, PhCH<sub>2</sub>) 3.38 (1H, dd,  $J$  = 14.8, 10.6, PhCH<sub>2</sub>) 3.88 (3H, s, OCH<sub>3</sub>) 4.91 (1H, m, CHNO<sub>2</sub>) 5.00 (1H, m, CHN) 5.03 – 5.06 (2H, m, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>) 5.74 (1H, ddt,  $J$  = 16.0, 11.4, 6.3, CH<sub>2</sub>CHCH<sub>2</sub>) 7.00 (2H, m, PMP-*H*) 7.15 (2H, m, Ar*H*) 7.20 (2H, d,  $J$  = 8.5, PMP-*H*) 7.27 – 7.30 (1H, m, Ar*H*) 7.30 – 7.34 (2H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  27.5 (CHNCH<sub>2</sub>) 30.3 (CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>) 37.8 (PhCH<sub>2</sub>) 55.7 (OCH<sub>3</sub>) 60.3 (CHN) 91.4 (CNO<sub>2</sub>) 114.7 (PMP-*C*) 114.9 (PMP-*C*) 116.3 (q,  $J$  = 288.6, CF<sub>3</sub>) 116.7 (CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>) 127.4 (q, ArCN) 127.9 (ArC) 128.6 (2C, ArC) 129.2 (2C, ArC) 130.4 (PMP-*C*) 131.0 (PMP-*C*) 134.6 (q, ArCCH<sub>2</sub>) 135.9 (CHCH<sub>2</sub>) 158.8 (q,  $J$  = 35.7, COCF<sub>3</sub>) 160.7 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.0 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 453 (96 %, M + NH<sub>4</sub><sup>+</sup>) 437 (100 %, M + H<sup>+</sup>); HRMS (C<sub>22</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 437.1688, found 437.1678.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*\*,2*R*\*)-1-nitro-1-phenylhex-5-en-2-yl)acetamide (352ac)**



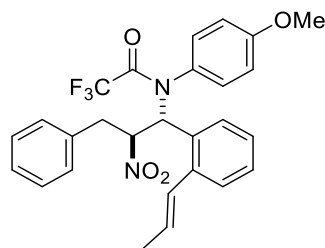
Prepared by *general procedure E* using  $\alpha$ -nitrotoluene **4a** (0.92 g, 6.73 mmol) and imine **82c** (1.44 g, 7.62 mmol). Purification by flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) and recrystallisation from Et<sub>2</sub>O/Hexanes afforded **352ac** as white crystals (1.56 g, 3.69 mmol, 55 %); mp 93 - 94 °C; IR  $\nu_{\text{max}}$  (thin film) 2936, 2838 (C-H) 1693 (C=O, amide) 1606, 1508, 1456 (C=C, Ar) 1552 (N-O, asym) 1357 (N-O, sym) 1150 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz, 60 °C)  $\delta$  1.70 – 1.80 (1H, m, CHNCH<sub>2</sub>) 2.09 – 2.40 (3H, m, CHNCH<sub>2</sub> & CHNCH<sub>2</sub>CH<sub>2</sub>) 3.79 (3H, s, OCH<sub>3</sub>) 5.08 (1H, dm, *J* = 10.2, CHCH<sub>2</sub>-cis) 5.11 (1H, dm, *J* = 17.2, CHCH<sub>2</sub>-trans) 5.31 (1H, br s, CHN) 5.72 (1H, br s, CHNO<sub>2</sub>) 5.84 (1H, ddt, *J* = 17.0, 10.3, 6.4, CH<sub>2</sub>CHCH<sub>2</sub>) 6.36 (1H, br s, PMP-*H*) 6.61 (1H, br s, PMP-*H*) 6.75 (2H, br m, PMP-*H*) 7.39 – 7.55 (5H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz, 60 °C)  $\delta$  28.8 (CHNCH<sub>2</sub>) 30.3 (CHNCH<sub>2</sub>CH<sub>2</sub>) 55.4 (OCH<sub>3</sub>) 92.5 (CHNO<sub>2</sub>) 114.2 (2C, PMP-C) 115.7 (q, *J* = 288.5, CF<sub>3</sub>) 116.2 (CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2</sub>) 128.7 (2C, ArC) 129.1 (2C, ArC) 130.1 (q, ArC) 130.7 (ArC) 131.8 (q, ArC) 136.0 (CH<sub>2</sub>CHCH<sub>2</sub>) 158.1 (q, *J* = 36.2, COCF<sub>3</sub>) 160.3 (ArCO) further signals indistinguishable; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.4 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 867 (6 %, 2M + Na<sup>+</sup>) 445 (23 %, M + Na<sup>+</sup>) 423 (M + H<sup>+</sup>) 376 (100 %, C<sub>21</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub>); HRMS (C<sub>21</sub>H<sub>22</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 423.1532, found 423.1522.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-3-phenyl-1-(2-vinylphenyl)propyl)acetamide (102ad)**



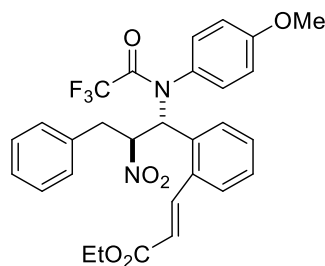
Prepared by *general procedure F* using *trans*- $\beta$ -nitrostyrene **64a** (1.00 g, 6.70 mmol) and imine **82d** (1.80 g, 7.60 mmol). Purification by recrystallisation (MeOH/Hexanes) afforded nitroacetamide **102ad** as a white solid (1.08 g, 2.22 mmol, 33 %); mp 128 – 130 °C; IR  $\nu_{\text{max}}$  (thin film) 1697 (C=O, amide) 1556 (N-O, asym) 1511 (C=C, Ar) 1325 (N-O, symm) 1182 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.55 (2H, m, CH<sub>2</sub>CHNO<sub>2</sub>) 3.80 (3H, s, OCH<sub>3</sub>) 5.45 (1H, d, *J* = 10.9, ArCHCH<sub>2</sub>-*cis*) 5.45 (1H, br s, CHNO<sub>2</sub>) 5.64 (1H, d, *J* = 17.2, ArCHCH<sub>2</sub>-*trans*) 6.07 (1H, br d, *J* = 6.1, PMP-*H*) 6.55 (1H, dd, *J* = 6.3, 2.8, PMP-*H*) 6.71 (2H, m, PMP-*H*, CHN) 6.91 (1H, dd, *J* = 8.7, 3.0, PMP-*H*) 6.96 (1H, t, *J* = 7.6, Ar*H*) 7.03 (1H, dd, *J* = 17.0, 11.0, ArCHCH<sub>2</sub>) 7.06 (1H, m, Ar*H*) 7.23 – 7.28 (3H, m, Ar*H*) 7.32 (1H, apt t, *J* = 7.2, Ar*H*) 7.37 (2H, apt t, *J* = 7.5, Ar*H*) 7.49 (1H, d, *J* = 7.8, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  38.4 (PhCH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 58.5 (CHNPMP) 89.4 (CNO<sub>2</sub>) 113.9 (PMP-C) 114.4 (PMP-C) 116.4 (q, *J* = 289.5) 119.2 (ArCHCH<sub>2</sub>) 126.9 (q, ArCN) 127.4 (ArC) 127.6 (PMP-C) 127.8 (ArC) 128.0 (ArC) 128.7 (2C, ArC) 129.3 (2C, ArC) 129.8 (ArC) 129.9 (q, ArCCHN) 130.0 (ArC) 132.6 (PMP-C) 133.7 (ArCHCH<sub>2</sub>) 134.7 (q, ArCCH<sub>2</sub>) 139.3 (q, ArCCHCH<sub>2</sub>) 158.0 (q, *J* = 35.6, CF<sub>3</sub>CO) 160.5 (ArCOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.0 ppm (3F, s, CF<sub>3</sub>); *m/z* (ES<sup>+</sup>) 507 (100%, M + Na<sup>+</sup>) 485 (80 %, M + H<sup>+</sup>) 438 (75 %, C<sub>26</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 485.1668, found 485.1688; Anal. Calcd. For C<sub>26</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>: C, 64.46; H, 4.79; N, 5.78; found: C, 64.46; H, 4.80; N, 5.76%.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-3-phenyl-1-(2-((*E*)-prop-1-en-1-yl)phenyl)propyl)acetamide (102ao)**



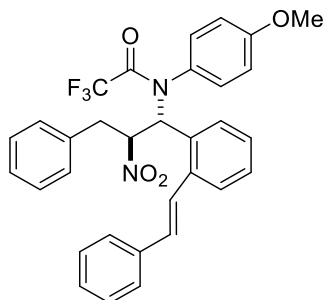
To a solution of aldehyde **102al** (111 mg, 0.23 mmol) and 3-pentanone (22  $\mu$ L, 0.21 mmol) in hexane (1 mL) was added  $\text{BF}_3 \cdot \text{OEt}_2$  (0.015 mL, 0.15 mmol) and the solution was refluxed for 90 mins and quenched with water (2 mL), extracted with  $\text{Et}_2\text{O}$  (5 mL x 3), dried and concentrated *in vacuo*. Purification by flash column chromatography (15 %  $\text{EtOAc}$ /hexanes) afforded **102ao** as a colourless yellow oil (63.5 mg, 0.13 mmol, 61 % yield); IR  $\nu_{\text{max}}$  (thin film) 2914, 2847 (C-H) 1694 (C=O, amide) 1554 (N-O, asym) 1509 (C=C, Ar) 1298 (N-O, sym) 1178 (C-F,  $\text{CF}_3$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  1.92 (3H, dd,  $J = 6.6, 1.5$ ,  $\text{CHCHCH}_3$ ) 3.54 – 3.58 (2H, m,  $\text{CH}_2$ ) 3.79 (3H, s,  $\text{OCH}_3$ ) 5.45 (1H, m,  $\text{CHNO}_2$ ) 6.07 (2H, m,  $\text{CHCHCH}_3$  & PMP- $H$ ) 6.55 (1H, dd,  $J = 8.9, 2.8$ , PMP- $H$ ) 6.67 – 6.77 (3H, m,  $\text{CHN}$ ,  $\text{CHCHCH}_3$  & Ar $H$ ) 6.91 (1H, dd,  $J = 8.7, 2.6$ , PMP- $H$ ) 6.92 (1H, m, Ar $H$ ) 7.06 (1H, apt d,  $J = 8.4$ , PMP- $H$ ) 7.23 (1H, td,  $J = 7.6, 0.5$ , Ar $H$ ) 7.25 – 7.27 (2H, m, Ar $H$ ) 7.30 – 7.39 (3H, m, Ar $H$ ) 7.40 (1H, d,  $J = 7.5$ , Ar $H$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  18.8 ( $\text{CHCH}_3$ ) 38.4 ( $\text{CH}_2$ ) 55.6 ( $\text{OCH}_3$ ) 58.8 ( $\text{CHN}$ ) 89.4 ( $\text{CHNO}_2$ ) 113.8 (PMP-C) 114.3 (PMP-C) 116.4 (q,  $J = 287.9$ ,  $\text{CF}_3$ ) 126.7 (ArC) 127.0 (q, ArCN) 127.5 (ArC) 127.6 (CH) 127.8 (ArC) 128.0 (ArC) 128.7 (2C, ArC) 129.2 (2C, ArC) 129.6 (q, ArCCHN) 129.6 (CH) 130.0 (PMP-C) 131.1 ( $\text{CHCHCH}_3$ ) 132.4 (PMP-C) 134.8 (q, ArCCH $_2$ ) 139.6 (q, ArCCHCHCH $_3$ ) 157.9 (q,  $J = 35.6$ ,  $\text{COCF}_3$ ) 160.4 (q, ArCO);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  - 67.2 ppm (3F, s,  $\text{CF}_3$ );  $m/z$  ( $\text{CI}^+$ ) 516 (76 %,  $\text{M} + \text{NH}_4^+$ ) 499 (100 %,  $\text{M} + \text{H}^+$ ) 452 (100 %,  $\text{C}_{27}\text{H}_{25}\text{F}_3\text{NO}_2^+$ ) 348 (20 %,  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{NO}_2^+$ ) 280 (18 %,  $\text{C}_{18}\text{H}_{18}\text{NO}_2^+$ ); HRMS ( $\text{C}_{27}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_4$ ) calcd. 499.1839, found 499.1839.

**ethyl (*E*)-3-(2-((1*R*\*,2*S*\*)-2-nitro-3-phenyl-1-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)propyl)phenyl)acrylate (**102an**)**



A solution of aldehyde **102aI** (0.48 g, 1.00 mmol) and (carbethoxymethylene)-triphenylphosphorane (0.35 g, 1.10 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under N<sub>2</sub> was stirred for 2 d, then concentrated *in vacuo*. Purification by flash column chromatography (20 % EtOAc/Hexanes) afforded **102an** as a mixture of isomers (85:10:5) as a colourless oil (0.17 g, 0.31 mmol, 31 %); IR  $\nu_{\max}$  (thin film) 2926 (C-H) 1967 (C=O, amide & ester) 1555 (N-O, asym) 1509 (C=C, Ar) 1366 (N-O, sym) 1154 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.39 (3H, t, *J* = 7.1, CH<sub>2</sub>CH<sub>3</sub>) 3.54 (1H, dd, *J* = 14.6, 10.6, CH<sub>2</sub>CHNO<sub>2</sub>) 3.60 (1H, dd, *J* = 14.6, 3.6, CH<sub>2</sub>CHNO<sub>2</sub>) 3.80 (3H, s, OCH<sub>3</sub>) 4.30 (2H, m, CH<sub>2</sub>CH<sub>3</sub>) 5.61 (1H, *br* s, CHNO<sub>2</sub>) 6.22 (1H, *br* m, PMP-*H*) 6.27 (1H, d, *J* = 15.5, CHCO<sub>2</sub>Et) 6.53 – 6.67 (2H, m, CH) 6.89 (1H, dd, *J* = 8.7, 2.8, PMP-*H*) 6.97 – 7.03 (2H, m, CH) 7.14 (1H, m, Ar*H*) 7.25 – 7.26 (2H, m, Ar*H*) 7.31 – 7.39 (4H, m, Ar*H*) 7.54 (1H, d, *J* = 7.8, Ar*H*) 7.92 (1H, *br* d, *J* = 15.0, CHCHCO<sub>2</sub>Et); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  14.3 (CH<sub>2</sub>CH<sub>3</sub>) 38.4 (PhCH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 59.6 (*br*, CHN) 60.9 (OCH<sub>2</sub>CH<sub>3</sub>) 89.4 (CHNO<sub>2</sub>) 113.9 (PMP-*C*) 114.8 (PMP-*C*) 116.3 (q, *J* = 288.6, CF<sub>3</sub>) 123.3 (CHCO<sub>2</sub>Et) 127.3 (q, *br*, ArCN) 127.8 (ArC) 128.1 (ArC) 128.3 (ArC) 128.7 (2C, ArC) 129.2 (2C, ArC) 129.8 (ArC) 130.0 (CH) 130.1 (CH) 131.8 (q, ArCCHN) 134.5 (q, ArCCH<sub>2</sub>) 135.7 (q, ArCCHCH) 140.4 (CHCHCO<sub>2</sub>Et) 157.8 (q, *J* = 35.8, COCF<sub>3</sub>) 160.6 (q, ArCO) 166.1 (q, CO<sub>2</sub>Et); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.1 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 579 (8 %, *M* + Na<sup>+</sup>) 574 (8 %, *M* + NH<sub>4</sub><sup>+</sup>) 557 (100 %, *M* + H<sup>+</sup>); HRMS (C<sub>29</sub>H<sub>28</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>) calcd. 557.1899, found 557.1901.

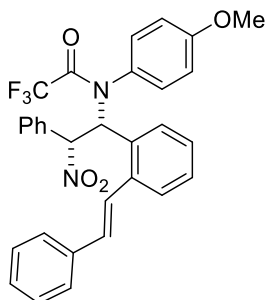
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-3-phenyl-1-(2-((*E*)-styryl)phenyl)propyl)acetamide (102g)**



Prepared by *general procedure F* using *trans*- $\beta$ -nitrostyrene **64a** (0.83 g, 5.55 mmol) and imine **82g** (1.95 g, 6.22 mmol). Purification by flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) afforded **102g** as a mixture of diastereomers (95:5) as a white solid (1.11 mg, 2.00 mmol, 36 %); mp 65 - 67 °C; IR  $\nu_{\text{max}}$  (thin film) 1695 (C=O, amide) 1556 (N-O, asymm) 1510 (C=C, Ar) 1301 (N-O, symm) 1181 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.58 (1H, dd, *J* = 14.6, 10.6, CH<sub>2</sub>) 3.61 (1H, dd, 14.6, 4.0, CH<sub>2</sub>) 3.77 (3H, s, OCH<sub>3</sub>) 5.53 (1H, br s, CHNO<sub>2</sub>) 6.18 (1H, br s, PMP-*H*) 6.58 (1H, dd, *J* = 8.8, 2.6, PMP-*H*) 6.81 (2H, br s, CH) 6.92 (1H, dd, *J* = 8.7, 2.8, PMP-*H*) 6.95 – 7.02 (2H, m, CH) 7.09 (1H, br d, *J* = 8.0, CH) 7.27 (2H, d, *J* = 7.2, CH) 7.30 – 7.35 (3H, m, CH) 7.36 – 7.44 (5H, m, CH) 7.57 (2H, d, *J* = 7.2, Ar*H*) 7.65 (1H, d, *J* = 7.6, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  38.4 (CH<sub>2</sub>) 55.5 (OCH<sub>3</sub>) 58.9 (CHN) 89.3 (CHNO<sub>2</sub>) 113.9 (PMP-C) 114.4 (PMP-C) 116.3 (q, *J* = 288.1, CF<sub>3</sub>) 124.4 (CH) 127.0 (CH) 127.0 (CH) 127.4 (CH) 128.0 (CH) 128.1 (CH) 128.3 (CH) 128.7 (4C, CH) 128.7 (CH) 128.9 (CH) 129.0 (CH) 129.3 (CH) 129.8 (CH) 130.0 (CH) 130.1 (q, C) 132.4 (q, C) 133.5 (CH) 134.7 (q, C) 136.9 (q, C) 138.6 (q, C) 158.0 (q, *J* = 35.9, COCF<sub>3</sub>) 160.5 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.1 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 583 (100 %, *M* + Na<sup>+</sup>); HRMS (C<sub>32</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>Na) calcd. 583.1821, found 583.1823.

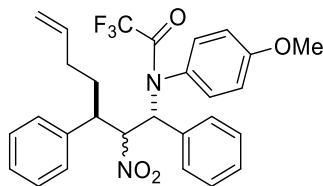


**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*R*\*)-2-nitro-2-phenyl-1-(2-((*E*)-styryl)phenyl)ethyl)acetamide (352ag)**



Prepared by *general procedure F* using  $\alpha$ -nitrotoluene **4a** (0.54 mL g, 4.50 mmol) and imine **82g** (1.60 g, 5.10 mmol). Purification by flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes followed by 10 – 20 % Et<sub>2</sub>O/Hexanes) afforded **352ag** as white crystals (276 mg, 0.51 mmol, 11 %); mp 153 – 155 °C; IR  $\nu_{\text{max}}$  (thin film) 1698 (C=O, amide) 1558 (N-O, asymm) 1511 (C=C, Ar) 1357 (N-O, symm) 1181 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.80 (3H, s, OCH<sub>3</sub>) 6.44 (2H, br s, CHNO<sub>2</sub> & PMP-*H*) 6.59 (1H, br s, CH) 6.68 (1H, dd, *J* = 8.8, 2.8, PMP-*H*) 6.79 (1H, d, *J* = 15.3, ArCHCH) 6.89 (1H, apt t, *J* = 6.4, CH) 6.95 (1H, dd, *J* = 8.8, 2.7, PMP-*H*) 7.15 – 7.24 (5H, m, CH) 7.28 – 7.34 (2H, m, CH) 7.37 (2H, d, *J* = 7.3, CH) 7.42 (2H, t, *J* = 7.7, CH) 7.47 – 7.58 (4H, m, CH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  55.6 (OCH<sub>3</sub>) 59.5 (CHN) 91.3 (CHNO<sub>2</sub>) 113.9 (PMP-C) 114.4 (PMP-C) 116.2 (q, *J* = 288.3, CF<sub>3</sub>) 124.9 (CH) 126.9 (2C, CH) 127.1 (2C, PMP-C) 128.3 (2C, CH) 128.8 (2C, CH) 128.9 (2C, CH) 129.0 (CH) 129.3 (CH) 129.7 (CH) 130.1 (q, CH) 130.3 (CH) 131.1 (q, CH) 131.3 (CH) 132.7 (q, CH) 133.6 (CH) 136.9 (q, CH) 138.6 (q, CH) 157.6 (q, *J* = 35.6, COCF<sub>3</sub>) 160.5 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.2 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 579 (22 %, M + CH<sub>3</sub>OH + H<sup>+</sup>) 569 (21 %, M + Na<sup>+</sup>) 564 (100 %, M + NH<sub>4</sub><sup>+</sup>) 547 (38 %, M + H<sup>+</sup>); HRMS (C<sub>31</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub>) calcd. 547.1845, found 547.1870.

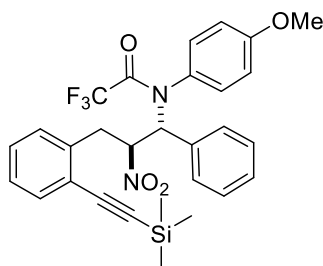
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,3*R*\*)-2-nitro-1,3-diphenylhept-6-en-1-yl)acetamide (102ra)**



A flask charged with Mg (39.2 mg, 1.60 mmol) was flame dried and stirred overnight under N<sub>2</sub> to activate the magnesium. Dry THF (2 mL) and a crystal of I<sub>2</sub> were added and the mixture heated to 70 °C. A portion of 4-bromobutene (0.03 mL, 0.30 mmol) was added to the reaction. After 50 min stirring at reflux, the rest of the bromide (0.12 mL, 1.20 mmol) in THF (1 mL) was added over 1 h at 0 °C, then the reaction was stirred at rt for 90 min to complete the generation of the Grignard reagent. The but-3-enyl magnesium bromide was added to a solution of *trans*-β-nitrostyrene **64a** (0.15 g, 1.00 mmol) and CuI (17.7 mg, 0.093 mmol) in DCM (5 mL) under N<sub>2</sub> at –78 °C over 7 min. The reaction was stirred at –78 °C for 0.5 h before addition of a solution of imine **82a** (340 mg, 1.60 mmol) in DCM (2.5 mL) to the reaction mixture at –78 °C. The reaction was stirred for 10 min before the addition of TFA (0.13 mL, 1.80 mmol) the reaction was then stirred for a further 1.5 h at –78 °C. The reaction was warmed for 5 min before the addition of sat. aq. NaHCO<sub>3</sub> solution (15 mL) giving a yellow colour. The product was extracted with Et<sub>2</sub>O (20 mL x 2), washed with brine (20 mL), dried (MgSO<sub>4</sub>) filtered and concentrated *in vacuo*. to give the crude nitroamine. The crude β-nitroamine was redissolved in dry DCM (10 mL) under N<sub>2</sub> and cooled to –78 °C. To the solution was added DIPEA (0.44 mL, 2.5 mmol) followed quickly by dropwise addition of TFAA (0.35 mL, 2.5 mmol). The reaction mixture was left to stir overnight and warm to rt and quenched on addition of 2M HCl (15 mL). The phases were separated and the aq. layer extracted with DCM (20 mL x 2), dried (MgSO<sub>4</sub>), filtered and conc *in vacuo*. Purification by flash column chromatography (5 % EtOAc/PE followed by 10 % EtOAc/Petrol) afforded **102ra** as a mixture of diastereomers (75:25) as a yellow oil (0.19 g, 0.37 mmol, 37 %); IR ν<sub>max</sub> (CDCl<sub>3</sub> cast) 2947 (C-H) 1697 (C=O) 1607, 1585 (Ar, C=C) 1552 (N-O) 1510 (Ar, C=C) 1254 (C-O) 1179, 1154 (CF<sub>3</sub>, C-F) 1033 (C-N) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) <sup>1</sup>H NMR δ<sub>major</sub> 1.81 – 2.10 (3H, m, CH<sub>2</sub>) 2.30 (1H, m, CH<sub>2</sub>) 3.49 (1H, dt, *J* = 12.5, 3.4, PhCHC<sub>4</sub>H<sub>7</sub>) 3.78 (3H, s, OCH<sub>3</sub>) 4.97 (1H, dd, *J* = 16.9, 1.3, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2-trans</sub>) 5.04 (1H, dd, *J* = 9.7, 0.7, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2-cis</sub>) 5.61 (1H, dd, *J* = 10.8, 4.2, CHNO<sub>2</sub>) 5.80 – 5.82

(1H, m, CH<sub>2</sub>CH) 6.20 (1H, apt d, *J* = 8.3, PMP-*H*) 6.35 (1H, d, *J* = 10.8, CHN) 6.60 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 6.87 (1H, dd, *J* = 8.7, 3.0, PMP-*H*) 7.03 (3H, m, PMP-*H* & Ar*H*) 7.45 – 7.19 (8H, m, Ar*H*); <sup>1</sup>H NMR δ<sub>minor</sub> 3.56 (1H, dt, *J* = 11.6, 3.1, PhCHC<sub>4</sub>H<sub>7</sub>) 3.81 (3H, s, OCH<sub>3</sub>) 5.09 (1H, dd, *J* = 10.2, 1.2, CH<sub>2</sub>CH<sub>2</sub>CHCH<sub>2-trans</sub>) 6.65 (1H, dd, *J* = 8.9, 2.9, PMP-*H*) further signals indistinguishable; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ<sub>major</sub> 23.9 (CH<sub>2</sub>) 28.3 (CH<sub>2</sub>) 44.9 (CHC<sub>4</sub>H<sub>7</sub>) 55.5 (OCH<sub>3</sub>) 62.4 (CHN) 91.7 (CNO<sub>2</sub>) 113.8 (PMP-C) 114.1 (PMP-C) 116.5 (CH<sub>2</sub>CH) 116.5 (q, CF<sub>3</sub>, *J* = 288.7) 127.5 (ArC) 128.1 (ArC) 128.2 (ArC) 128.4 (ArC) 128.7 (ArC) 128.8 (ArC) 128.9 (ArC) 129.3 (ArC) 129.5 (ArC) 130.5 (ArC) 132.4 (ArC) 133.4 (q, ArC) 134.8 (q, ArC) 137.0 (ArC) 137.3 (CH<sub>2</sub>CH) 138.8 (q, ArC) 158.5 (q, *J* = 35.5, COCF<sub>3</sub>) 160.4 (q, ArCO); <sup>19</sup>F (CDCl<sub>3</sub>, 282 MHz) δ -67.5 (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 513 (42 %, M + H<sup>+</sup>) 466 (100 %, C<sub>28</sub>H<sub>27</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 308 (52 %, C<sub>16</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 294 (22 %, C<sub>19</sub>H<sub>20</sub>NO<sub>2</sub><sup>+</sup>) 220 (32 %, C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 145 (22 % C<sub>11</sub>H<sub>13</sub><sup>+</sup>) HRMS C<sub>28</sub>H<sub>28</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> calcd. 513.2001 found 513.2006.

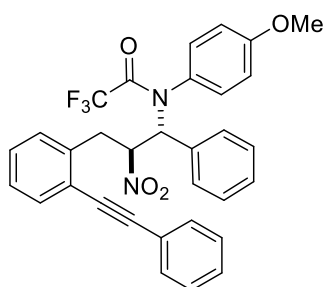
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-1-phenyl-3-(2-(trimethylsilyl)ethynyl)phenyl)propyl)acetamide (102va)**



Prepared by *general procedure F* using nitroalkene **64v** (2.28 g, 9.30 mmol) and imine **82a** (2.28 g, 10.0 mmol). Purification by flash column chromatography (50 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes followed by 5 % EtOAc/Petrol) afforded **102va** as a white solid (3.06 g, 5.52 mmol, 58 %); mp 49 – 51 °C; IR ν<sub>max</sub> (thin film) 2962 (C-H) 2155 (C-C, alkyne) 1698 (C=O, amide) 1556 (N-O, asymm) 1300 (N-O, symm) 1179, 1153 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 0.32 (9 H, s, OSi(CH<sub>3</sub>)<sub>3</sub>) 3.72 (1H, dd, *J* = 14.5, 4.0, ArCH<sub>2</sub>) 3.81 (1H, dd, *J* = 14.8, 10.5, ArCH<sub>2</sub>) 3.81 (3H, s, OCH<sub>3</sub>) 5.79 (1H, apt t, *J* = 8.6, CHNO<sub>2</sub>) 6.13 (1H, d, *J* = 7.3) 6.38 (1H, d, *J* = 6.2, PMP-*H*) 6.67 (1H, dd, *J* = 8.9, 2.7, PMP-*H*) 6.89 (1H, dd, *J* = 8.7, 2.8, PMP-*H*) 7.10 (2H, d, *J* = 7.5, Ar*H*) 7.13 (1H, d, *J* = 8.6, Ar*H*) 7.23 (2H, apt d, *J* = 7.8, Ar*H*) 7.26 (2H, apt d, *J* = 8.8, Ar*H*) 7.29 – 7.33 (2H, m, Ar*H*) 7.54 (1H, d, *J* = 7.7, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 0.05 (Si(CH<sub>3</sub>)<sub>3</sub>) 36.5 (CH<sub>2</sub>Ar) 55.6 (ArCOCH<sub>3</sub>) 65.8 (CHN) 88.0 (CNO<sub>2</sub>) 100.1 (q, CSi(CH<sub>3</sub>)<sub>3</sub>) 102.9 (CCSi)

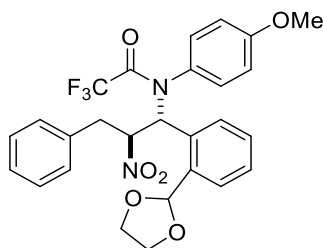
114.1 (PMP-C) 114.3 (PMP-C) 116.3 (q,  $J = 288.3$ ,  $\text{CF}_3$ ) 123.3 (q) 127.8 (ArC) 128.3 (q, PMP-CN) 128.8 (ArC) 128.9 (ArC) 129.3 (ArC) 129.5 (ArC) 129.7 (ArC) 130.6 (ArC) 132.1 (PMP-C) 133.3 (q) 133.8 (ArC) 136.3 (q) 158.1 (q,  $J = 36.0$ ,  $\text{CF}_3\text{CO}$ ) 160.4 (ArCOCH<sub>3</sub>);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  - 67.1 ppm (3F, s,  $\text{CF}_3$ );  $m/z$  (EI) 554 (10 %,  $\text{M}^+$ ) 508 (7 %,  $\text{C}_{29}\text{H}_{29}\text{F}_3\text{NO}_2\text{Si}$ ) 217 (10 %,  $\text{C}_9\text{H}_7\text{F}_3\text{NO}_2$ ); HRMS ( $\text{C}_{29}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_4\text{Si}$ ) calcd. 554.1849, found 554.1827.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*S*\*)-2-nitro-1-phenyl-3-(2-phenylethynyl)phenyl)propyl)acetamide (102wa)**



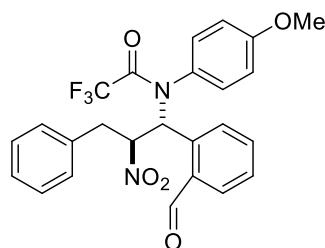
Prepared by *general procedure F* using nitroalkene **64w** (4.23 g, 17.0 mmol) and imine **82a** (4.06 g, 19.2 mmol). Purification by trituration in MeOH afforded **102wa** as a mixture of isomers (90:10 *anti:syn*, 6.17 g, 11.1 mmol, 65 %). Further recrystallisation ( $\text{Et}_2\text{O}$ /Hexanes followed  $\text{CH}_2\text{Cl}_2$ /Hexanes x 2) afforded *anti*-**102wa** as a white solid (3.60 g, 6.44 mmol, 38 %); mp 160 – 162 °C; IR  $\nu_{\text{max}}$  (thin film) 1696 (C=O, amide) 1556 (N-O, asym) 1509, 1495 (C=C, Ar) 1300 (N-O, sym) 1180, 1153 (C-F,  $\text{CF}_3$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  3.62 (3H, s,  $\text{OCH}_3$ ) 3.73 (1H, dd,  $J = 14.1$ , 11.3,  $\text{CH}_2$ ) 3.91 (1H, dd,  $J = 14.1$ , 3.8,  $\text{CH}_2$ ) 5.71 (1H, dt,  $J = 11.0$ , 3.8,  $\text{CHNO}_2$ ) 6.07 – 6.17 (2H, m, PMP-*H*) 6.44 (1H, d,  $J = 9.1$ ,  $\text{CHN}$ ) 6.49 (1H, dd,  $J = 8.8$ , 2.8, PMP-*H*) 7.00 (2H, d,  $J = 7.6$ , Ar*H*) 7.17 – 7.23 (3H, m, Ar*H*) 7.25 – 7.29 (2H, m, PMP-*H* & Ar*H*) 7.30 – 7.33 (2H, m, Ar*H*) 7.40 – 7.44 (Ar*H*) 7.61 – 7.67 (Ar*H*);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  37.0 ( $\text{CH}_2$ ) 55.5 ( $\text{OCH}_3$ ) 64.4 ( $\text{CHN}$ ) 87.7 (q, CC) 88.2 ( $\text{CHNO}_2$ ) 94.1 (CC) 113.2 (PMP-C) 114.5 (PMP-C) 116.3 (q,  $J = 288.4$ ,  $\text{CF}_3$ ) 122.9 (q, ArCCC) 122.9 (ArCCC) 127.3 (q, ArCN) 128.1 (ArC) 128.7 (2C, ArC) 128.8 (2C, ArC) 128.9 (ArC) 129.4 (ArC) 129.5 (2C, ArC) 129.7 (ArC) 129.9 (ArC) 130.6 (ArC) 132.1 (2C, PMP-C) 132.4 (ArC) 132.9 (ArCCHN) 133.6 (ArC) 135.8 (q, ArCCH<sub>2</sub>) 158.3 (q,  $J = 35.6$ ,  $\text{COCF}_3$ ) 160.2 (q, ArCO);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  - 67.0 (3F, s,  $\text{CF}_3$ );  $m/z$  (EI) 558 (100 %,  $\text{M}^+$ ) 190 (84 %,  $\text{C}_{15}\text{H}_{11}$ ); HRMS ( $\text{C}_{32}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4$ ) calcd. 558.1766, found 558.1734.

***N*-((1*R*\*,2*S*\*)-1-(2-(1,3-dioxolan-2-yl)phenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**102am**)**

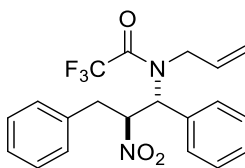


Prepared by *general procedure F* using *trans*- $\beta$ -nitrostyrene **64a** (0.30 g, 2.00 mmol) and imine **82m** (2.26 mmol). Purification by flash column chromatography (40 - 60 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) afforded **102am** as a white solid (0.51 g, 0.96 mmol, 48 %); mp 109 - 110 °C; IR  $\nu_{\text{max}}$  (thin film) 2890 (C-H) 1696 (C=O, amide) 1554 (N-O asymm) 1509 (C=C, Ar) 1299 (N-O, symm) 1180 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.55 - 3.60 (2H, m, CH<sub>2</sub>) 3.78 (3H, s, OCH<sub>3</sub>) 4.01 - 4.23 (4H, m, OCH<sub>2</sub>CH<sub>2</sub>O) 5.37 (1H, ddd, *J* = 10.9, 9.5, 5.0, CHNO<sub>2</sub>) 5.99 (1H, s, CHO<sub>2</sub>) 6.16 (1H, dd, *J* = 8.8, 2.1, PMP-*H*) 6.47 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 6.61 (1H, d, *J* = 7.9, Ar*H*) 6.93 (1H, dd, *J* = 8.7, 3.0, PMP-*H*) 6.99 - 7.03 (2H, m, CHN & Ar*H*) 7.14 (1H, dd, *J* = 8.7, 2.6, PMP-*H*) 7.23 - 7.40 (6H, m, Ar*H*) 7.69 (1H, dd, *J* = 7.8, 1.2, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  38.4 (ArCH<sub>2</sub>) 55.5 (OCH<sub>3</sub>) 56.7 (CHN) 65.3 (OCH<sub>2</sub>CH<sub>2</sub>O) 65.4 (OCH<sub>2</sub>CH<sub>2</sub>O) 89.5 (CHNO<sub>2</sub>) 101.2 (CHO<sub>2</sub>) 113.6 (PMP-C) 114.1 (PMP-C) 116.5 (q, *J* = 288.5, CF<sub>3</sub>) 126.8 (q, ArCN) 127.6 (ArC) 128.0 (ArC) 128.4 (ArC) 128.7 (2C, ArC) 128.8 (ArC) 129.2 (2C, ArC) 129.6 (ArC) 130.0 (PMP-C) 131.1 (q, ArCCHN) 133.2 (PMP-C) 135.0 (q, ArCCH<sub>2</sub>) 136.7 (q, ArCCHO<sub>2</sub>) 158.1 (q, *J* = 35.5, COCF<sub>3</sub>) 160.3 (ArCOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.4 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 531 (100 %, M + H<sup>+</sup>) 484 (43 %, C<sub>27</sub>H<sub>25</sub>F<sub>3</sub>NO<sub>4</sub>) 440 (6 %, C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>); HRMS (C<sub>27</sub>H<sub>26</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>) calcd. 531.1738, found 531.1737.

**2,2,2-trifluoro-*N*-((1*R*\*,2*S*\*)-1-(2-formylphenyl)-2-nitro-3-phenylpropyl)-*N*-(4-methoxyphenyl)acetamide (102al)**



A solution of nitroacetamide **102am** (1.42 g, 2.69 mmol) and FeCl<sub>3</sub>/SiO<sub>2</sub> (0.29 g, 5 % by weight) in acetone (64 mL) and the reaction was stirred for 30 h. Additional portions of FeCl<sub>3</sub>/SiO<sub>2</sub> (2 x 0.14 g) were added after 6 h and 24 h until there was no further conversion. The reaction mixture was filtered through celite and concentrated in *vacuo*. Purification by flash column chromatography (15 – 25 % EtOAc/Hexanes) followed by recrystallisation (CHCl<sub>3</sub>/Hexanes) afforded **102al** as a white solid (1.08 g, 2.22 g, 82 %); mp 90 - 92 °C; IR  $\nu_{\text{max}}$  (thin film) 2836 (C-H) 1692 (C=O, amide, aldehyde overlapped) 1604, 1508, 1454 (C=C, Ar) 1553 (N-O, asym) 1300 (N-O, sym) 1150 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.55 (1H, dd, *J* = 14.6, 10.4, CH<sub>2</sub>) 3.59 (1H, dd, *J* = 14.5, 4.0, CH<sub>2</sub>) 3.81 (3H, s, OCH<sub>3</sub>) 5.81 (1H, td, *J* = 10.4, 3.5, CHNO<sub>2</sub>) 6.48 (1H, br d, *J* = 7.8, PMP-*H*) 6.71 (1H, dd, *J* = 8.9, 2.8, PMP-*H*) 6.86 (1H, dd, *J* = 8.7, 2.8, PMP-*H*) 6.90 (1H, apt d, *J* = 8.5, PMP-*H*) 7.17 (1H, d, *J* = 10.8, CHN) 7.26 (2H, d, *J* = 7.5, Ar*H*) 7.29 – 7.39 (4H, m, Ar*H*) 7.42 (1H, td, *J* = 7.7, 1.2, Ar*H*) 7.52 (1H, td, *J* = 7.5, 1.0, Ar*H*) 7.84 (1H, dd, *J* = 7.7, 1.3, Ar*H*) 10.12 (1H, s, CHO); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  38.5 (CH<sub>2</sub>) 55.6 (OCH<sub>3</sub>) 58.7 (CHN) 90.2 (CHNO<sub>2</sub>) 114.0 (PMP-*C*) 114.9 (PMP-*C*) 116.2 (q, *J* = 289.0, CF<sub>3</sub>) 128.1 (2C, ArC) 128.1 (q, ArCN) 128.8 (2C, ArC) 129.2 (ArC) 129.7 (ArC) 130.1 (PMP-*C*) 130.2 (ArC) 131.8 (PMP-*C*) 133.1 (ArC) 133.9 (ArC) 134.1 (q, ArC) 134.6 (q, ArC) 134.7 (q, ArC) 158.1 (q, *J* = 36.0, COCF<sub>3</sub>) 160.6 (ArCOCH<sub>3</sub>) 191.3 (CHO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.2 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 504.2 (15 %, *M* + NH<sub>4</sub><sup>+</sup>) 487.2 (100 %, *M* + H<sup>+</sup>) 440.2 (7 %, C<sub>25</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>3</sub>); HRMS (C<sub>25</sub>H<sub>22</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>) calcd. 487.1481, found 487.1472.

***N*-allyl-2,2,2-trifluoro-*N*-((1*R*\*,2*S*\*)-2-nitro-1,3-diphenylpropyl)acetamide (102at)**

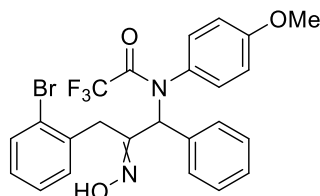
Prepared by *general procedure F* using trans- $\beta$ -nitrostyrene **64a** (1.50 g, 10.0 mmol) and imine **82t** (2.91 g, 20.0 mmol). Purification via flash column chromatography (40 % CH<sub>2</sub>Cl<sub>2</sub>/Hexanes followed by 20 % Et<sub>2</sub>O/Hexanes) afforded **102at** as a mixture of diastereomers (75:25) as a yellow oil (1.53 g, 3.90 mmol, 39 %); mp<sub>anti</sub> 90 - 91 °C; IR<sub>anti</sub>  $\nu_{\text{max}}$  (thin film) 3029 (C-H) 1691 (C=O, amide) 1555 (N-O, asym) 1454 (C=C, Ar) 1146 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{anti}}$  3.16 (2H, m, CH<sub>2</sub>Ph) 3.86 (1H, dd,  $J$  = 16.3, 7.2, CH<sub>2</sub>N) 4.14 (1H, dd,  $J$  = 16.3, 5.8, CH<sub>2</sub>N) 5.22 (1H, d,  $J$  = 10.6, CHN) 5.51 (2H, m, CH<sub>2</sub>CHCH<sub>2</sub>N) 5.88 (1H, ddt,  $J$  = 17.0, 10.2, 6.7, CHCH<sub>2</sub>N) 6.07 (1H, ddd,  $J$  = 10.7, 9.6, 5.0, CHNO<sub>2</sub>) 7.17 (2H, m, ArH) 7.26 – 7.38 (6H, m, ArH) 7.46 (2H, m, ArH); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{syn}}$  2.85 (1H, dd,  $J$  = 14.7, 3.0, CH<sub>2</sub>Ph) 3.01 (1H, dd,  $J$  = 14.8, 11.1, CH<sub>2</sub>Ph) 3.93 – 4.04 (2H, m, CH<sub>2</sub>N) 4.96 (1H, d,  $J$  = 11.0, CHN) 5.33 (2H, m, CH<sub>2</sub>CHCH<sub>2</sub>N) 5.65 (1H, ddt,  $J$  = 17.0, 10.0, 6.4, CHCH<sub>2</sub>N) 6.26 (1H, td,  $J$  = 11.0, 3.0, CHNO<sub>2</sub>) 7.03 (2H, m, ArH) further signals indistinguishable; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta_{\text{anti}}$  38.0 (ArCH<sub>2</sub>) 50.9 (CH<sub>2</sub>N) 64.8 (CHN) 91.0 (CHNO<sub>2</sub>) 116.4 (q,  $J$  = 288.1, CF<sub>3</sub>) 122.2 (CH<sub>2</sub>CHCH<sub>2</sub>N) 127.9 (ArC) 128.8 (2C, ArC) 129.1 (2C, ArC) 129.1 (2C, ArC) 129.4 (ArC) 129.9 (ArC) 132.0 (ArC) 134.0 (q, ArC) 134.6 (q, ArC) 157.8 (q,  $J$  = 36.4, COCF<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 68.9 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 410 (100 %, M + NH<sub>4</sub><sup>+</sup>); HRMS (C<sub>20</sub>H<sub>19</sub>F<sub>3</sub>O<sub>3</sub>N<sub>2</sub> + NH<sub>4</sub><sup>+</sup>) calcd. 410.1686, found 410.1685.

**3.3.7 Nef reactions****3.3.7.1 Preparation of oximes**

**General procedure G:** To a solution of Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (2.08 g, 6.96 mmol) in 6M HCl (31 mL) under N<sub>2</sub> was added Zn dust (3.54 g, 54.2 mmol) (EXOTHERMIC!) and the reaction was stirred until blue (formation of CrCl<sub>2</sub>). The solution of CrCl<sub>2</sub> (33 mL) was added to a refluxing solution of  $\beta$ -nitroacetamide (1.00 mmol) in methanol (31 mL) under N<sub>2</sub> and the mixture was stirred for 1 h. The reaction mixture was cooled and concentrated *in vacuo*. to half the reaction volume. The mixture was extracted with DCM (40 mL x 2), washed with sat. aq. NaCO<sub>3</sub> solution (40 mL), brine (50 mL), dried (MgSO<sub>4</sub>), filtered and

concentrated *in vacuo*. Purification was carried out via flash column chromatography or recrystallisation.

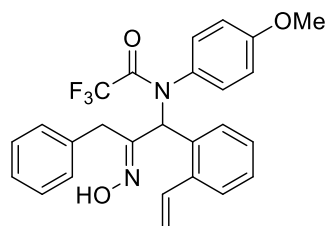
***N*-(3-(2-bromophenyl)-2-(hydroxyimino)-1-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (359)**



Prepared by *general procedure G* using  $\beta$ -nitroacetamide **102ba** (0.13 g, 0.24 mmol). Purification by flash column chromatography (10 % EtOAc/Hexanes) and recrystallization (PhMe/hexanes) afforded **359** as colourless white crystals (0.12 g, 0.23 mmol, 96 %); mp 145 - 147 °C; IR  $\nu_{\max}$  (thin film) 3414 (O-H) 1678 (C=N & C=O overlapping) 1608, 1586, 1509 (C=C, Ar) 1151 (CF<sub>3</sub> C-F) 1025 (CHN) 947 (N-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  3.37 (1H, d, *J* = 16.1, CH<sub>2</sub>Ar) 3.74 (3H, s, OCH<sub>3</sub>) 4.23 (1H, d, *J* = 16.1, CH<sub>2</sub>Ar) 6.16 (1H, s, CHN) 6.21 (1H, dd, *J* = 8.8, 2.2, ArH) 6.40 (1H, dd, *J* = 8.0, 3.0, ArH) 6.79 (1H, dd, *J* = 9.0, 5.0, ArH) 6.87 (2H, d, *J* = 7.1, ArH) 7.04 – 7.26 (8H, dm, ArH) 7.60 (1H, dd, *J* = 7.7, 1.4, ArH) 7.46 (1H, dd, *J* = 8.0, 1.2, ArH) 7.70 (1H, dd, *J* = 8.7, 2.1, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  33.3 (CH<sub>2</sub>Ar) 55.3 (OCH<sub>3</sub>) 66.0 (CHN) 113.1 (2C, ArC) 124.9 (ArC) 127.6 (ArC) 128.3 (2C, ArC) 128.4 (ArC) 128.6 (ArC) 128.8 (ArC) 130.9 (ArC) 131.1 (2C, ArC) 132.5 (ArC) 132.6 (ArC) 132.7 (2C, ArC) 135.0 (ArC) 155.3 (q, C=NOH) 159.5 (q), further signals indistinguishable; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.7 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 521 + 523 (1:1, 100 %, M + H) 487 + 489 (0.8:1, 11 %, C<sub>24</sub>H<sub>19</sub>BrF<sub>3</sub>NO<sub>2</sub><sup>+</sup> or C<sub>23</sub>H<sub>17</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup>) 439 (10 %, C<sub>24</sub>H<sub>20</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup>) 308 (27 %, C<sub>16</sub>H<sub>13</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 302 + 304 (0.8:1, 74 %, C<sub>15</sub>H<sub>13</sub>BrNO<sup>+</sup>) 220 (C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>); HRMS (C<sub>24</sub>H<sub>21</sub>F<sub>3</sub>(<sup>79</sup>Br)N<sub>2</sub>O<sub>3</sub>) calcd. 521.06876, found 521.06933.

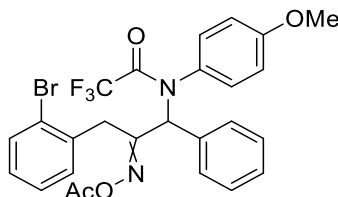


**(E)-2,2,2-trifluoro-N-(2-(hydroxyimino)-3-phenyl-1-(2-vinylphenyl)propyl)-N-(4-methoxyphenyl)acetamide (403)**



Prepared by *general procedure G* using  $\beta$ -nitroacetamide **102da** (0.83 g, 1.71 mmol). Purification by flash column chromatography (10 - 20 % EtOAc/Hexanes) and recrystallisation (toluene/hexanes) afforded **403** as a white solid (0.35 g, 0.75 mmol, 44 %); mp 133 - 135 °C; IR  $\nu_{\text{max}}$  (thin film) 3414 (O-H) 2836 (C-H) 1675 (C=O, amide & C=N oxime) 1509 (C=C, Ar) 1185, 1152 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.00 (1H, d,  $J$  = 15.7, PhCH<sub>2</sub>) 3.69 (3H, s, OCH<sub>3</sub>) 4.30 (1H, d,  $J$  = 15.7, PhCH<sub>2</sub>) 5.30 (1H, dd,  $J$  = 11.0, 1.2, ArCHCH<sub>2</sub>-*cis*) 5.57 (1H, dd,  $J$  = 17.2, 1.2, ArCHCH<sub>2</sub>-*trans*) 6.19 (1H, dd,  $J$  = 8.8, 2.4, PMP-*H*) 6.33 (1H, dd,  $J$  = 8.8, 3.1, PMP-*H*) 6.47 (1H, br s, CHN) 6.54 (1H, dd,  $J$  = 17.2, 11.0, ArCHCH<sub>2</sub>) 6.61 (1H, dd,  $J$  = 7.8, 1.2, ArH) 6.73 (1H, dd,  $J$  = 8.8, 3.0, PMP-*H*) 6.90 (1H, td,  $J$  = 7.6, 1.2, ArH) 7.06 (2H, m, ArH) 7.14 – 7.23 (4H, m, ArH) 7.37 (1H, dd,  $J$  = 7.8, 1.2, ArH) 7.43 (1H, s, N-OH) 7.70 (1H, dd,  $J$  = 8.9, 2.5, PMP-*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  33.2 (ArCH<sub>2</sub>) 55.3 (OCH<sub>3</sub>) 60.4 (CHN) 112.9 (2C, PMP-C) 116.4 (q,  $J$  = 290.3, CF<sub>3</sub>) 118.5 (CH<sub>2</sub>CHAr) 126.4 (ArC) 126.8 (ArC) 127.5 (ArC) 128.6 (q, ArCN) 128.6 (2C, ArC) 129.0 (ArC) 129.4 (2C, ArC) 130.0 (q, ArCCHN) 131.1 (ArC) 131.7 (PMP-C) 132.6 (PMP-C) 133.1 (CH<sub>2</sub>CHAr) 135.3 (q, ArCCH<sub>2</sub>) 139.0 (q, ArCCHCH<sub>2</sub>) 156.2 (q, CNOH) 157.0 (q,  $J$  = 34.7, COCF<sub>3</sub>) 159.4 (ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.2 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 469 (82 %, M + H<sup>+</sup>) 250.2 (100 %, C<sub>17</sub>H<sub>16</sub>NO<sup>+</sup>); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>) calcd. 469.17390, found 469.173518.

***N*-(2-(acetoxymimino)-3-(2-bromophenyl)-1-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (387)**



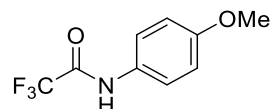
To a solution of oxime **359** (225 mg, 0.43 mmol) in dry THF (6 mL) at 0 °C under N<sub>2</sub> was added NEt<sub>3</sub> (0.12 mL, 0.86 mmol) followed by AcCl (0.07 mL, 0.95 mmol) and the reaction stirred to rt over 24 h. The reaction was quenched by pouring into H<sub>2</sub>O (40 mL), extracted with EtOAc (250 mL x 3) washed with H<sub>2</sub>O (25 mL), brine (35 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15 % EtOAc/Hexanes) afforded **387** as an orange oil (215 mg, 0.38 mmol, 89 %); IR  $\nu_{\text{max}}$  (thin film) 1771 (C=O, ester) 1691 (C=O, amide) 1510 (C=C, Ar) 1183 (C-F, CF<sub>3</sub>)cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.20 (1H, s, OCOCH<sub>3</sub>) 3.52 (1H, d, *J* = 16.1, CH<sub>2</sub>) 3.69 (3H, s, ArOCH<sub>3</sub>) 4.15 (1H, d, *J* = 16.1, CH<sub>2</sub>) 6.11 (1H, dd, *J* = 8.7, 2.7, PMP-*H*) 6.20 (1H, s, CHN) 6.33 (1H, dd, *J* = 8.7, 3.0, PMP-*H*) 6.82 – 6.85 (3H, m, Ar*H*) 7.04 – 7.10 (3H, m, Ar*H*) 7.17 (1H, apt t, *J* = 7.5, Ar*H*) 7.22 (1H, td, *J* = 7.5, 1.0, Ar*H*) 7.27 (1H, dd, *J* = 7.7, 1.4, Ar*H*) 7.43 (1H, dd, *J* = 8.1, 0.9, PMP-*H*) 8.14 (1H, dd, *J* = 8.9, 2.2, PMP-*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  19.8 (COCH<sub>3</sub>) 35.5 (ArCH<sub>2</sub>) 55.3 (OCH<sub>3</sub>) 65.2 (CHN) 113.0 (PMP-C) 113.2 (PMP-C) 116.4 (q, *J* = 288.7, CF<sub>3</sub>) 125.0 (q, ArCBr) 127.8 (ArC) 128.1 (q, ArCCHN) 128.6 (2C, ArC) 128.9 (ArC) 129.2 (ArC) 131.1 (ArC) 131.2 (2C, ArC) 131.3 (q, ArCN) 132.4 (PMP-C) 132.8 (ArC) 133.7 (PMP-C) 134.0 (q, ArCCH<sub>2</sub>) 157.4 (q, *J* = 35.6, CF<sub>3</sub>CO) 159.6 (q, ArCO) 162.3 (q, CNOAc) 168.0 (q, CO<sub>2</sub>N); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.4 ppm (3F, s, CF<sub>3</sub>); *m/z* (CI<sup>+</sup>) 564 + 566 (1:1, 6 %, M + H<sup>+</sup>), 308 (100 %, C<sub>16</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>); HRMS (C<sub>26</sub>H<sub>23</sub>(<sup>79</sup>Br)F<sub>3</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup>) calcd. 563.07933, found 563.078312.

### 3.3.7.2 Nef reaction by-products

**General Procedure H:** To a solution of  $\beta$ -nitroacetamide **102aa** (50 mg, 0.11 mmol) in dry MeOH (5 mL) under N<sub>2</sub> at rt was added a freshly prepared solution of 1M NaOMe solution in dry MeOH (0.14 mL, 0.14 mmol) and the reaction stirred at rt or 50 °C until complete by TLC. The reaction was quenched upon addition of 2M HCl (2 mL) (or *conc* H<sub>2</sub>SO<sub>4</sub>) partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>, washed with sat. aq. NaCl solution (30

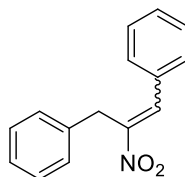
mL), dried (MgSO<sub>4</sub>) filtered and concentrated *in vacuo*. Purification by flash column chromatography (5 % Et<sub>2</sub>O/hexanes) afforded a range of by-products.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (364)**



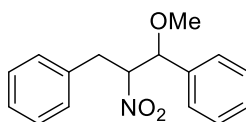
Isolated as a byproduct from *general procedure H*. Purification by flash column chromatography (5 % Et<sub>2</sub>O/hexanes) afforded **364** as a pale yellow solid (26.3 mg, 0.11 mmol, 100 % recovery); mp 110-111 °C (lit<sup>294</sup> 110-111 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 3.84 (3H, s, OCH<sub>3</sub>) 6.94 (2H, apt d, *J* = 9.0, ArH) 7.50 (2H, apt d, *J* = 9.1, ArH) 7.77 (1H, br s, NH). NMR data consistent with published data.<sup>294</sup>

**2-nitroprop-1-ene-1,3-diyl dibenzene (363)**



Isolated as a byproduct from *general procedure H*. Purification by flash column chromatography (5 % Et<sub>2</sub>O/hexanes) afforded **363** as a pale yellow solid (6.1 mg, < 5 % recovery); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 4.28 (2H, s, CH<sub>2</sub>) 7.23 (2H, dm, *J* = 7.9, ArH) 7.27 (1H, m, ArH) 7.34 (2H, m, ArH) 7.41 – 7.47 (5H, m, ArH) 8.33 (1H, s, CHCNO<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 33.1 (CH<sub>2</sub>) 127.1 (ArC) 127.8 (2C, ArC) 129.1 (2C, ArC) 129.3 (2C, ArC) 129.8 (2C, ArC) 130.6 (ArC) 132.1 (q, ArC) 135.7 (CHCNO<sub>2</sub>) 136.3 (q, ArC) 149.7 (q, CNO<sub>2</sub>). NMR data in agreement with published data.<sup>295</sup>

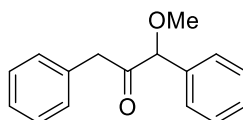
**(1-methoxy-2-nitropropane-1,3-diyl)dibenzene (361)**



Isolated as a byproduct from *general procedure H*. Purification by flash column chromatography (5 % Et<sub>2</sub>O/hexanes) afforded **361** as a mixture of diastereoisomers (60:40) as a colourless oil (15.4 mg, 0.057 mmol, 53 %). IR ν<sub>max</sub> (thin film) 3058, 2926, 2918 (C-H) 1516 (N-O, asymm) 1493 (C=C, Ar) 1318 (N-O, symm) cm<sup>-1</sup>; <sup>1</sup>H NMR

(CDCl<sub>3</sub>, 500 MHz)  $\delta_{\text{major}}$  2.60 (1H, dd,  $J = 14.6, 3.1$ , CH<sub>2</sub>) 3.04 (1H, dd,  $J = 14.5, 11.4$ , CH<sub>2</sub>) 3.19 (3H, s, OCH<sub>3</sub>) 4.59 (1H, d,  $J = 9.5$ , CHOMe) 4.88 (1H, ddd,  $J = 11.7, 9.5, 3.2$ , CHNO<sub>2</sub>) 6.96 (2H, dd,  $J = 7.4, 1.8$ , ArH) 7.18 – 7.24 (3H, m, ArH) 7.40 – 7.48 (5H, m, ArH);  $\delta_{\text{minor}}$  3.31 (3H, s, OCH<sub>3</sub>) 3.35 (1H, dd,  $J = 15.4, 3.6$ , CH<sub>2</sub>) 3.39 (1H, dd,  $J = 15.4, 10.0$ , CH<sub>2</sub>) 4.65 (1H, d,  $J = 7.1$ , CHOMe) 4.84 (1H, ddd,  $J = 9.8, 7.0, 3.5$ , CHNO<sub>2</sub>) 7.11 – 7.29 (2H, apt d,  $J = 6.9$ , ArH) 7.21 – 7.29 (3H, mArH) 7.33 – 7.41 (5H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta_{\text{minor}}$  35.3 (CH<sub>2</sub>) 57.5 (OCH<sub>3</sub>) 83.8 (CH) 94.0 (CH) 127.3 (ArC) 127.3 (2C, ArC) 127.8 (2C, ArC) 128.9 (2C, ArC) 128.9 (2C, ArC) 129.1 (ArC) 136.0 (q, ArC) 136.2 (q, ArC); m/z (CI<sup>+</sup>) 289 (100 %, M + NH<sub>4</sub><sup>+</sup>) 242 (40 %, C<sub>16</sub>H<sub>17</sub>O + NH<sub>4</sub><sup>+</sup>); HRMS (C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub> + NH<sub>4</sub><sup>+</sup>) calcd. 289.1547, found 289.1548.

### 1-methoxy-1,3-diphenylpropan-2-one (362)

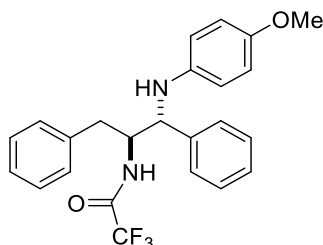


To a solution of  $\beta$ -nitroacetamide **102aa** (114 mg, 0.25 mmol) in anhydrous MeOH (1.5 mL) was added NaOMe (freshly prepared NaOMe 0.5 mmol in 1.0 mL MeOH). The mixture was cooled to  $-78\text{ }^{\circ}\text{C}$  and O<sub>3</sub> was bubbled through (no blue colour obtained). The reaction mixture was flushed with N<sub>2</sub> to remove excess O<sub>3</sub>, followed by the addition of Me<sub>2</sub>S (0.25 mL, 3.40 mmol) and the reaction was stirred and warmed to rt overnight under N<sub>2</sub>. The reaction material was concentrated *in vacuo*. Purification by flash column chromatography (5-15 % EtOAc/hexanes) afforded pure **362** as a colourless oil (32 mg, 0.13 mmol, 53 %); IR  $\nu_{\text{max}}$  (thin film) 1723 (C=O), 1602, 1494, 1453 (C=C, Ar) 1092, 1073 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.35 (3H, s, OCH<sub>3</sub>) 3.71 (1H, d,  $J = 16.0$ , PhCH<sub>2</sub>) 3.82 (1H, d,  $J = 16.0$ , PhCH<sub>2</sub>) 4.77 (1H, s, CHOCH<sub>3</sub>) 7.07 (2H, d,  $J = 7.6$ , ArH) 7.23 (1H, apt t,  $J = 7.5$ , ArH) 7.27 (2H, apt t,  $J = 7.5$ , ArH) 7.33-7.41 (5H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  44.6 (CH<sub>2</sub>) 57.4 (CH<sub>3</sub>) 88.7 (PhCO) 127.0 (ArC) 127.4 (ArC) 128.6 (ArC) 128.9 (ArC) 129.0 (ArC) 129.8 (ArC) 133.8 (q, ArC) 135.6 (q, ArC) 205.7 (CH<sub>2</sub>CO); m/z (CI<sup>+</sup>) 241 (22 %, M + H<sup>+</sup>) 209 (77 %, C<sub>15</sub>H<sub>13</sub>O<sup>+</sup>) 121 (100 %, C<sub>8</sub>H<sub>9</sub>O<sup>+</sup>); HRMS (C<sub>16</sub>H<sub>17</sub>O<sub>2</sub><sup>+</sup>) calcd. 241.12285, found 241.121744.

### 3.3.8 Reduction of $\beta$ -nitro-2,2,2-trifluoroacetamides

#### 3.3.8.1 Preparation of 1,2-aminoacetamides

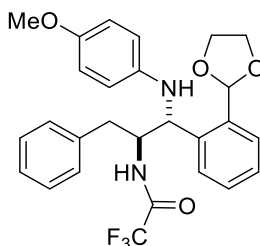
##### 2,2,2-trifluoro-*N*-((1*R*\*,2*S*\*)-1-((4-methoxyphenyl)amino)-1,3-diphenylpropan-2-yl)acetamide (**101aa**)



To a solution of  $\beta$ -nitroacetamide **102aa** (0.46 g, 1.00 mmol) in EtOAc (40 mL) and EtOH (40 mL) at 0 °C was added 6 M aq. HCl (42 mL). The colourless solution was vigorously stirred and Zn dust (3.23 g, 49.4 mmol) was added in three portions. The grey suspension was removed from the cold bath and allowed to warm to rt over 2 h to give a colourless solution. Zn dust (1.60 g, 24.5 mmol) was added in one portion and the reaction mixture was stirred at rt for 1 h. The EtOH and EtOAc were removed *in vacuo* and the aqueous solution was neutralised by the addition of NaHCO<sub>3</sub>(s). The neutralized aqueous layer was extracted with EtOAc (3 x 250 mL), the combined organic phases were washed with 2M HCl (400 mL), brine (400 mL), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The product was then redissolved in EtOH (40 mL), to this was added 6M HCl (5 mL) and the mixture was stirred for 2 h. EtOH was removed *in vacuo*. To this was added H<sub>2</sub>O (40 mL) and the aqueous phase was extracted with EtOAc (100 mL x 3) washed with brine (120 mL) dried (MgSO<sub>4</sub>) filtered and conc *in vacuo*. Purification by column chromatography (10 - 30 % EtOAc/Hexanes) afforded **101aa** as a white solid (307 mg, 0.72 mmol, 72 %); mp 145 - 146 °C; IR  $\nu_{\text{max}}$  (thin film) 3325, 2930 (C-H) 1700 (C=O, amide) 1510 (C=C. Ar) 1155 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.71 (1H, dd, *J* = 14.2, 9.0, PhCH<sub>2</sub>) 3.0 (1H, dd, *J* = 14.2, 5.4, PhCH<sub>2</sub>) 3.69 (3H, s, OCH<sub>3</sub>) 4.29 (1H, br s, NHPMP) 4.60 (1H, d, *J* = 3.9, CHNHPMP) 4.74 (1H, m, CHCH<sub>2</sub>) 6.28 (1H, br d, *J* = 9.3, NHTFA) 6.47 (2H, dm, *J* = 8.9, PMP-*H*) 6.69 (2H, dm, *J* = 9.0, PMP-*H*) 7.15 (2H, apt d, *J* = 7.4, Ar*H*) 7.26 (1H, m, Ar*H*) 7.30 – 7.42 (7H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.8 (PhCH<sub>2</sub>) 55.7 (CHCH<sub>2</sub>) 55.8 (OCH<sub>3</sub>) 61.5 (CHN) 114.9 (2C, PMP-C) 115.3 (2C, PMP-C) 117.7 (q, *J* = 288.0, CF<sub>3</sub>) 127.3 (ArC) 127.5 (2C, ArC) 128.3 (ArC) 129.0 (2C, ArC) 129.1 (2C, ArC) 129.1 (2C, ArC) 136.4 (q, ArCN) 138.4 (q, ArCCH<sub>2</sub>) 140.5

(q, ArCCHN) 152.7 (q, ArCO) 157.5 (q,  $J = 37.0$ , CF<sub>3</sub>CO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 76.1 ppm (3F, s, CF<sub>3</sub>); m/z (CI<sup>+</sup>) 429 (61 %, M + H<sup>+</sup>) 306 (29 %, C<sub>17</sub>H<sub>15</sub>F<sub>3</sub>NO<sup>+</sup>) 212 (100 %, C<sub>14</sub>H<sub>14</sub>NO<sup>+</sup>); HRMS (C<sub>24</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup>) calcd. 429.17844, found 429.178308.

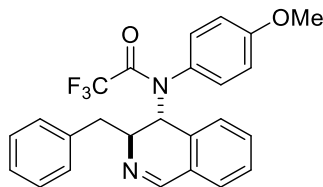
**N-((1R\*,2S\*)-1-(2-(1,3-dioxolan-2-yl)phenyl)-1-((4-methoxyphenyl)amino)-3-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (101am)**



To a solution of **102am** (0.49 g, 0.94 mmol) in MeOH (8 mL) under N<sub>2</sub> at 0 °C was added NiCl<sub>2</sub>6H<sub>2</sub>O (0.22 g, 0.94 mmol) followed by NaBH<sub>4</sub> (0.18 g, 4.76 mmol), reaction stirred until complete by TLC. The reaction was quenched on addition of sat. aq. NH<sub>4</sub>Cl solution (13 mL), extracted with EtOAc (20 mL x 3), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through a pad of silica and concentrated *in vacuo*. Purification of the product by recrystallisation (Et<sub>2</sub>O/Hexanes) afforded **101am** as a white solid (170 mg, 0.34 mmol, 36 %); mp 166 – 168 °C; IR  $\nu_{\max}$  (thin film) 3373, 3250 (N-H) 3029, 2955, 2899 2834 (C-H) 1714 (C=O, amide) 1511 (C=C, Ar) 1182 1158 (C-F, CF<sub>3</sub>)cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  3.15 (1H, dd,  $J = 13.7, 4.3$ , CH<sub>2</sub>Ph) 3.31 (1H, m, OCH<sub>2</sub>CH<sub>2</sub>O) 3.37 (1H, dd,  $J = 13.8, 4.1$ , CH<sub>2</sub>Ph) 3.69 (3H, s, OCH<sub>3</sub>) 3.72 – 3.79 (3H, m, OCH<sub>2</sub>CH<sub>2</sub>O) 4.07 (1H, *br s*, NHPMP) 4.28 (1H, m, CHNTFA) 4.87 (1H, d,  $J = 10.4$ , CHNPMP) 5.61 (1H, s, CHO<sub>2</sub>) 6.65 (2H, dm,  $J = 9.0$ , PMP-*H*) 6.70 (2H, dm,  $J = 9.1$ , PMP-*H*) 7.20 (3H, m, ArH) 7.27 – 7.36 (5H, m, ArH) 7.47 (1H, d,  $J = 7.6$ , ArH) 8.20 (1H, d,  $J = 8.8$ , NHTFA); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.8 (CH<sub>2</sub>Ph) 53.0 (CHNPMP) 55.7 (OCH<sub>3</sub>) 55.8 (CHNTFA) 64.5 ((OCH<sub>2</sub>)<sub>2</sub>) 64.8 ((OCH<sub>2</sub>)<sub>2</sub>) 104.8 (CHO<sub>2</sub>) 114.9 (2C, PMP-*C*) 115.2 (2C, PMP-*C*) 115.8 (q,  $J = 288.2$ , CF<sub>3</sub>) 126.0 (ArC) 127.0 (ArC) 127.7 (ArC) 128.6 (3C, ArC) 130.7 (2C, ArC) 130.9 (ArC) 132.9 (q, ArC) 136.4 (q, ArCCH<sub>2</sub>) 140.2 (q, ArCN) 140.4 (q, ArC) 152.6 (q, ArCO) 156.5 (q,  $J = 37.1$ , COCF<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 76.3 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 517 (8 %, M + NH<sub>4</sub><sup>+</sup>) 501 (100 %, M + H<sup>+</sup>) ; HRMS (C<sub>27</sub>H<sub>28</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub><sup>+</sup>) calcd. 501.2001, found 501.1999.

### 3.3.8.2 Preparation of cyclic imine **551**

#### *N*-((3*S*\*,4*R*\*)-3-benzyl-3,4-dihydroisoquinolin-4-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**551**)



To a solution of  $\beta$ -nitroacetamide **102am** (1.02 g, 1.89 mmol) and dry DIPEA (1.70 mL, 9.76 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (14 mL) at  $-10^\circ\text{C}$  was added dropwise  $\text{HSiCl}_3$  (0.70 mL, 6.93 mmol) and the reaction was stirred to rt over 24 h. The reaction was quenched with sat. aq.  $\text{NaHCO}_3$  solution (50 mL) followed by extraction with EtOAc (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. Purification by flash column chromatography on basic alumina (10 – 40 % EtOAc/Hexanes) afforded **551** as a colourless oil (0.16 g, 0.37 mmol, 19 %); IR  $\nu_{\text{max}}$  (thin film) 2914, 2837 (C-H) 1685 (C=O, amide & C=N) 1508, 1453 (C=C, Ar) 1145 (C-F,  $\text{CF}_3$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  2.52 (1H, dd,  $J = 13.8, 8.3$ ,  $\text{CH}_2$ ) 2.90 (1H, dd,  $J = 13.8, 6.6$ ,  $\text{CH}_2$ ) 3.71 (3H, s,  $\text{OCH}_3$ ) 4.67 (1H, apt ddm,  $J = 8.0, 6.8$ ,  $\text{CH}_2\text{CHN}$ ) 5.94 (1H, s,  $\text{CHNMPMP}$ ) 5.95 (1H, m,  $\text{PMP-H}$ ) 6.39 (1H, dd,  $J = 8.8, 2.9$ ,  $\text{PMP-H}$ ) 6.75 (1H, dd,  $J = 8.8, 2.9$ ,  $\text{PMP-H}$ ) 7.10 (1H, d,  $J = 7.5$ ,  $\text{ArH}$ ) 7.14 (1H, dd,  $J = 8.7, 2.4$ ,  $\text{PMP-H}$ ) 7.17 – 7.25 (3H, m,  $\text{ArH}$ ) 7.28 – 7.32 (2H, m,  $\text{ArH}$ ) 7.41 (1H, td,  $J = 7.4, 1.4$ ,  $\text{ArH}$ ) 7.49 (1H, d,  $J = 7.5$ ,  $\text{ArH}$ ) 7.53 (1H, td,  $J = 7.5, 1.2$ ,  $\text{ArH}$ ) 7.82 (1H, s,  $\text{HC=N}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  39.7 ( $\text{CH}_2$ ) 53.3 ( $\text{CHNMPMP}$ ) 55.4 ( $\text{OCH}_3$ ) 63.1 ( $\text{CH}_2\text{CHNCHN}$ ) 113.3 (2C,  $\text{PMP-C}$ ) 116.5 (q,  $J = 288.8$ ,  $\text{CF}_3$ ) 126.9 ( $\text{ArC}$ ) 127.4 ( $\text{ArC}$ ) 127.6 (q,  $\text{ArCNTFA}$ ) 128.6 (q,  $\text{ArCCHNCHCH}_2$ ) 128.6 (2C,  $\text{ArC}$ ) 129.4 (2C,  $\text{ArC}$ ) 129.9 ( $\text{ArC}$ ) 130.0 (q,  $\text{ArCCHNMPMP}$ ) 130.3 ( $\text{ArC}$ ) 131.1 ( $\text{PMP-C}$ ) 131.8 ( $\text{PMP-C}$ ) 132.4 ( $\text{ArC}$ ) 137.4 (q,  $\text{ArCCH}_2$ ) 156.7 (q,  $J = 35.1$ ,  $\text{COCF}_3$ ) 157.7 ( $\text{HCNCHCH}_2$ ) 159.9 ( $\text{ArCOCH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  – 66.9 ppm (3F, s,  $\text{CF}_3$ );  $m/z$  (EI) 438 (5 %,  $\text{M}^+$ ) 220 (59 %,  $\text{C}_{16}\text{H}_{14}\text{N}^+$ ); HRMS ( $\text{C}_{25}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_2$ ) calcd. 438.15496, found 438.15491.

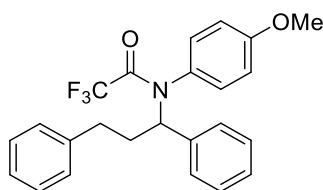
### 3.3.9 Radical denitration - Preparation of 2,2,2-trifluoroacetamides

**General Procedure I:** To a solution of  $\beta$ -nitroacetamide (1 mmol) in benzene (48 mL) under  $\text{N}_2$  at rt were added AIBN (0.3 mmol) and  $\text{Bu}_3\text{SnH}$  (10 mmol) and the reaction mixture was degassed. The reaction mixture was heated to reflux for 6 hours or until no change observed by TLC. The reaction mixture was cooled to rt, concentrated. *in vacuo*.

The reaction mixture was taken up in MeCN/Hexane (50:50, 20 mL). The MeCN/Hexane layers were partitioned, with extraction of the Hexane layer with MeCN (10 mL x 2). The combined MeCN extracts were washed with Hexane (20 mL x 3) and the MeCN layer was concentrated *in vacuo*. The crude product was purified by flash column chromatography (0 – 10 % Et<sub>2</sub>O). In some cases recrystallization afforded single separation of diastereomers.

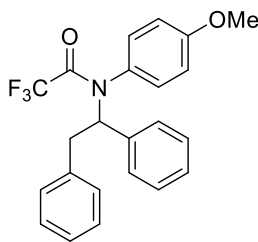
### 3.3.10 Protodenitration

#### *N*-(1,3-diphenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**413**)<sup>181b</sup>

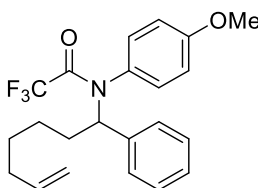


Prepared by *modified general procedure I* using  $\beta$ -nitroacetamide **102aa** (20.0 mg, 0.044 mmol, 1 eq), Bu<sub>3</sub>SnH (0.12 mL, 0.45 mmol, 10 eq) and AIBN (5.0 mg, 0.030 mmol, 0.7 eq) in PhMe (1.0 mL) at reflux under N<sub>2</sub> for 15 min. Purification by flash column chromatography (0 – 10% Et<sub>2</sub>O/Pet. ether) afforded **413** as a colourless oil (12.7 mg, 0.031 mmol, 79 %); IR  $\nu_{\text{max}}$  (CDCl<sub>3</sub> cast) cm<sup>-1</sup> 2931, 2854 (C-H) 1687 (C=O, amide) 1606, 1585, 1510, 1455 (C=C, Ar) 1182, 1148 (C-F, CF<sub>3</sub>) <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.19 (2H, m, CH<sub>2</sub>CHN) 2.68 (2H, dm, CH<sub>2</sub>Ph) 3.79 (3H, s, OCH<sub>3</sub>) 6.03 (1H, t, *J* = 7.7, CHN) 6.08 (1H, dd, *J* = 8.8, 2.5, ArH) 6.57 (1H, dd, *J* = 8.8, 3.0, ArH) 6.87 (1H, dd, *J* = 8.6, 3.1, ArH) 7.10 (2H, apt d, *J* = 6.8, ArH) 7.17 – 7.18 (3H, m, ArH) 7.21 (1H, apt t, *J* = 7.4, ArH) 7.26 – 7.31 (5H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  32.6 (CH<sub>2</sub>) 32.8 (CH<sub>2</sub>) 55.5 (OCH<sub>3</sub>) 59.9 (CHN) 113.5 (PMP-C) 113.5 (PMP-C) 116.7 (q, *J* = 289.1, CF<sub>3</sub>) 126.3 (ArC) 126.8 (q, ArC) 128.5 (ArC) 128.5 (2C, ArC) 128.6 (2C, ArC) 128.7 (2C, ArC) 129.2 (2C, ArC) 131.4 (CH) 132.5 (CH) 137.6 (q, ArC) 141.2 (q, ArC) 157.5 (q, *J* = 35.0, COCF<sub>3</sub>) 160.0 (q, ArCO); <sup>19</sup>F (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.4 ppm (3F, s, CF<sub>3</sub>); *m/z* (CI<sup>+</sup>) 414 (91 %, *M* + H<sup>+</sup>) 220 (100 %, C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 195 (42 %, C<sub>15</sub>H<sub>15</sub><sup>+</sup>) HRMS (C<sub>24</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>2</sub>) calcd 414.16809 found 414.167626.



***N*-(1,2-diphenylethyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (503)**

Prepared by *general procedure I* using  $\beta$ -nitroacetamide **352aa** (99.0 mg, 0.22 mmol). Purification (10 % Et<sub>2</sub>O in Hexanes) afforded **503** as a colourless oil (63.2 mg, 0.16 mmol, 71 %); IR  $\nu_{\text{max}}$  (thin film) 2839 (C-H) 1687 (C=O, amide) 1511, 1454 (C=C, Ar) 1182, 1150 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  3.21 (1H, dd,  $J$  = 14.5, 7.4, PhCH<sub>2</sub>) 3.36 (1H, dd,  $J$  = 14.6, 8.7, PhCH<sub>2</sub>) 3.79 (3H, s) 6.04 (1H, dd,  $J$  = 8.8, 2.1, PMP-*H*) 6.19 (1H, apt t,  $J$  = 8.1, CHN) 6.58 (1H, dd,  $J$  = 8.8, 2.9, PMP-*H*) 6.83 (1H, dd,  $J$  = 8.8, 2.9, PMP-*H*) 6.96 (1H, dd,  $J$  = 8.7, 1.7, PMP-*H*) 7.19-7.32 (10H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.6 (CH<sub>2</sub>) 55.5 (OCH<sub>3</sub>) 61.9 (CHN) 113.5 (PMP-C) 113.6 (PMP-C) 116.5 (q,  $J$  = 289.2, CF<sub>3</sub>) 126.8 (2C, ArC) 127.9 (q, 2C, ArCN) 128.5 (2C, ArC) 128.7 (2C, ArC) 129.1 (2C, ArC) 129.2 (2C, ArC) 131.4 (PMP-C) 131.9 (PMP-C) 137.3 (q, ArCCHN) 137.6 (ArCCH<sub>2</sub>) 157.4 (q,  $J$  = 34.5, COCF<sub>3</sub>) 160.0 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  -67.3 ppm (3F, s, CF<sub>3</sub>);  $m/z$  (CI<sup>+</sup>) 400 (100 %, M + H<sup>+</sup>) 308 (25 %, C<sub>16</sub>H<sub>31</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 181 (46 %, C<sub>14</sub>H<sub>13</sub><sup>+</sup>); HRMS (C<sub>23</sub>H<sub>21</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 400.15244, found 400.152075.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-phenylhept-6-en-1-yl)acetamide (416)**

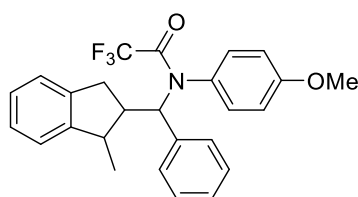
Prepared by *modified general procedure I* using  $\beta$ -nitroacetamide **102ca** (33.8 mg, 0.078 mmol), AIBN (10.0 mg, 0.054 mmol, 0.7 eq) and Bu<sub>3</sub>SnH (0.11 mL, 0.42 mmol, 10 eq) in PhMe (1 mL) at reflux for 1 h. Purification by flash column chromatography (10 % Et<sub>2</sub>O in petroleum ether) afforded **416** as a colourless oil (18.3 mg, 0.047 mmol, 60 %) IR  $\nu_{\text{max}}$  (thin film) cm<sup>-1</sup> 2925, 2855 (C-H) 1691 (C=O, amide) 1608, 1585, 1511 (C=C, Ar) 1184, 1152 (C-F, CF<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.45 (3H, m, CH<sub>2</sub>) 1.85 (3H, m, CH<sub>2</sub>) 2.05 (2H, q,  $J$  = 6.5, CH<sub>2</sub>) 3.79 (3H, s, OCH<sub>3</sub>) 4.94 (1H, apt dd,  $J$  = 10.2, 1.9)

4.99 (1H, apt dd,  $J = 17.3, 1.9$ , CHCH<sub>2</sub>) 5.78 (1H, m, CHCH<sub>2</sub>) 5.96 (1H, t,  $J = 7.8$ , CHN) 6.05 (1H, dd,  $J = 8.8, 2.7$ ) 6.54 (1H, dd,  $J = 8.7, 3.1$ ) 6.88 (1H, dd,  $J = 8.8, 2.8$ , ArH) 7.07 (2H, m, ArH) 7.16 – 7.25 (3H, m, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  25.9 (CH<sub>2</sub>) 28.8 (CH<sub>2</sub>) 30.3 (CH<sub>2</sub>) 33.6 (CH<sub>2</sub>) 55.5 (OCH<sub>3</sub>) 60.0 (CHN) 113.3 (PMP-C) 113.4 (PMP-C) 114.8 (CH<sub>2</sub>CHR) 116.72 (q,  $J = 289.1$ , CF<sub>3</sub>) 126.8 (ArC) 128.4 (2C, ArC) 129.1 (2C, ArC) 130.0 (q, ArC) 131.4 (PMP-C) 132.5 (PMP-C) 138.0 (q, ArC) 138.7 (CH<sub>2</sub>CHCH<sub>2</sub>) 157.4 (q,  $J = 35.3$ , COCF<sub>3</sub>) 159.9 (q, ArCO); m/z (CI<sup>+</sup>) 392 (100 %, M + H<sup>+</sup>) 220 (26 %, C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>NO<sub>2</sub><sup>+</sup>) 173 (76 %, C<sub>13</sub>H<sub>17</sub><sup>+</sup>) HRMS (C<sub>22</sub>H<sub>25</sub>F<sub>3</sub>NO<sub>2</sub>) calcd 392.18374 found 392.181913.

### 3.3.11 Intramolecular radical addition to an alkene

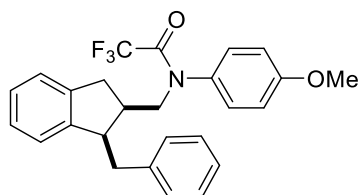
#### 3.3.11.1 Formation of indanes

##### 2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1-methyl-2,3-dihydro-1*H*-inden-2-yl)(phenyl)methyl)acetamide (**420**)



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102da** (51.5 mg, 0.11 mmol). Purification using flash column chromatography (0 – 10 % Et<sub>2</sub>O/Hexanes) afforded **420** as a mixture of diastereoisomers as a colourless oil (16.7 mg, 0.038 mmol, 38 %); IR  $\nu_{\max}$  (thin film) 3019, 2931, 2836 (C-H) 1685 (C=O, amide) 1604, 1582, 1509 (C=C, Ar) 1180, 1146 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data display a complex mixture; m/z (ESI<sup>+</sup>) 462 (100 %, M + H<sup>+</sup>); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>2</sub>Na) calcd. 462.1639, found 462.1657.

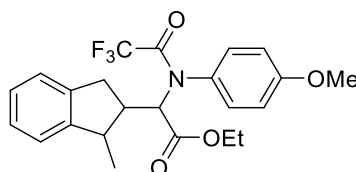
##### *N*-(((1*R*\*,2*R*\*)-1-benzyl-2,3-dihydro-1*H*-inden-2-yl)methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**421**)



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102da** (51.5 mg, 0.11 mmol). Purification using flash column chromatography (0 – 10 % Et<sub>2</sub>O/Hexanes) afforded **421**

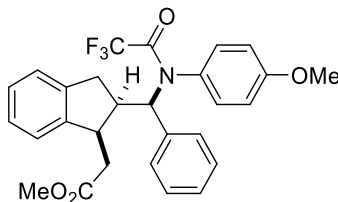
as a colourless oil (8.6 mg, 0.020 mmol, 20 %); IR  $\nu_{\max}$  (thin film) 2923 (C-H) 1694 (C=O, amide) 1511 (C=C, Ar) 1152 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.62 (1H, dd,  $J$  = 13.3, 10.3, CH<sub>2</sub>Ph) 2.72 (1H, m, CHCH<sub>2</sub>N) 2.90 (1H, dd, 13.4, 6.0, CH<sub>2</sub>Ph) 2.93 (2H, d,  $J$  = 8.1, CH<sub>2</sub>CHCH<sub>2</sub>N) 3.36 (1H, dt,  $J$  = 10.2, 6.5, CHCHCH<sub>2</sub>N) 3.74 (1H, dd,  $J$  = 13.3, 5.3, CH<sub>2</sub>N) 3.84 (3H, s, OCH<sub>3</sub>) 4.31 (1H, dd,  $J$  = 13.3, 9.8, CH<sub>2</sub>N) 6.42 (1H, d,  $J$  = 7.5, ArH) 6.87 – 6.92 (2H, m, PMP-H) 6.94 (1H, td,  $J$  = 7.5, 1.0, ArH) 6.96 – 7.00 (2H, m, ArH) 7.13 (1H, td,  $J$  = 7.5, 0.9, ArH) 7.14 – 7.25 (6H, m PMP-H & ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  35.2 (CH<sub>2</sub>CHCH<sub>2</sub>N) 35.4 (CH<sub>2</sub>Ph) 41.5 (CHCH<sub>2</sub>N) 48.0 (CHCH<sub>2</sub>Ph) 52.0 (CH<sub>2</sub>N) 55.6 (OCH<sub>3</sub>) 115.0 (2C, br, PMP-C) 116.6 (q,  $J$  = 284.9, CF<sub>3</sub>) 124.7 (ArC) 125.0 (ArC) 125.8 (ArC) 126.2 (ArC) 126.9 (ArC) 128.3 (2C, ArC) 129.4 (2C, ArC) 130.0 (2C, br, PMP-C) 131.2 (q, ArCN) 139.8 (q, ArCCH<sub>2</sub>) 141.8 (q, ArCCH<sub>2</sub>) 145.6 (q, ArCCHCH<sub>2</sub>Ph) 157.5 (q,  $J$  = 34.9, COCF<sub>3</sub>) 159.9 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 66.9 ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 440 (100 %, M + H<sup>+</sup>); HRMS (C<sub>26</sub>H<sub>25</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 440.1837, found 440.1821.

**ethyl 2-(1-methyl-2,3-dihydro-1H-inden-2-yl)-2-(2,2,2-trifluoro-N-(4-methoxyphenyl)acetamido)acetate (449)**



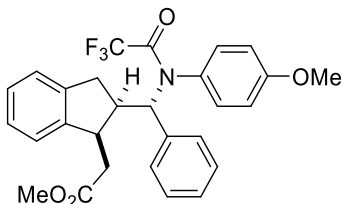
Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102df** (0.30 g, 0.63 mmol). Purification via flash column chromatography (0 – 10 % Et<sub>2</sub>O/Hexanes) afforded **449** as a mixture of isomers as a colourless oil (66.9 mg, 0.15 mmol, 24 %); IR  $\nu_{\max}$  (thin film) 2957, 2933, 2839 (C-H) 1739 (C=O, ester) 1694 (C=O, amide) 1509 (C=C, Ar) 1149 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data display a complex mixture; m/z (CI<sup>+</sup>) 453 (100 %, M + NH<sub>4</sub><sup>+</sup>) 436 (6 %, M + H<sup>+</sup>); HRMS (C<sub>23</sub>H<sub>25</sub>F<sub>3</sub>NO<sub>4</sub>) calcd. 436.1730, found 436.17298.

**methyl 2-((1*R*\*,2*R*\*)-2-((*R*\*)-phenyl(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)methyl)-2,3-dihydro-1*H*-inden-1-yl)acetate (**470a**)**



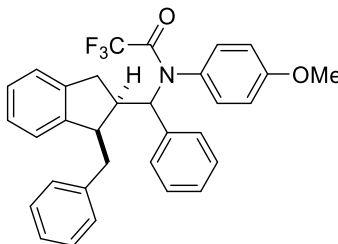
Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ea** (0.50 g, 0.92 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **470** as a mixture of diastereoisomers, further recrystallisation (CH<sub>2</sub>Cl<sub>2</sub>/hexanes) afforded **470a** as a white solid (140 mg, 0.28 mmol, 31 %); mp 152 – 153 °C; IR  $\nu_{\text{max}}$  (thin film) 2954 (C–H) 1735 (C=O, ester) 1688 (C=O, amide) 1511 (C=C, Ar) 1184, 1154 (C–F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.41 (1H, dd,  $J$  = 15.2, 10.9, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>) 2.54 (2H, d,  $J$  = 9.5, ArCH<sub>2</sub>CHCHN) 2.96 (1H, dd,  $J$  = 15.2, 4.0, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>) 3.07 (1H, m, CHCHN) 3.70 (3H, s, COOCH<sub>3</sub>) 3.80 (3H, s, ArOCH<sub>3</sub>) 3.94 (1H, ddd,  $J$  = 10.9, 6.8, 4.0, ArCHCH<sub>2</sub>COOCH<sub>3</sub>) 6.07 (1H, dd,  $J$  = 9.0, 1.9, PMP-*H*) 6.15 (1H, d,  $J$  = 12.1, CHN) 6.61 (1H, dd,  $J$  = 8.8, 3.0, PMP-*H*) 6.92 (1H, dd,  $J$  = 8.8, 3.0, PMP-*H*) 7.04 (1H, m, Ar*H*) 7.12 – 7.16 (4H, m, Ar*H*) 7.25 (1H, d,  $J$  = 5.5, Ar*H*) 7.29 – 7.37 (3H, m, Ar*H*) 7.49 (1H, dd,  $J$  = 8.8, 2.1, PMP-*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  35.2 (CH<sub>2</sub>CO) 35.7 (ArCH<sub>2</sub>) 42.4 (ArCHCH<sub>2</sub>CO) 43.6 (CHCHN) 51.8 (COOCH<sub>3</sub>) 55.5 (ArOCH<sub>3</sub>) 60.3 (CHN) 113.4 (PMP-*C*) 113.7 (PMP-*C*) 116.6 (q,  $J$  = 288.4, CF<sub>3</sub>) 124.6 (Ar*C*) 124.7 (Ar*C*) 126.2 (q, ArCN) 126.8 (Ar*C*) 127.4 (Ar*C*) 128.5 (2*C*, Ar*C*) 128.8 (Ar*C*) 129.8 (2*C*, Ar*C*) 131.2 (PMP-*C*) 133.2 (PMP-*C*) 137.3 (q, ArCCHN) 141.2 (q, ArCCH<sub>2</sub>) 146.1 (q, ArCCHCH<sub>2</sub>CO) 158.0 (q,  $J$  = 35.2, COCF<sub>3</sub>) 160.2 (q, ArCOCH<sub>3</sub>) 173.1 (CO<sub>2</sub>CH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 66.9 (3F, s, CF<sub>3</sub>);  $m/z$  (CI<sup>+</sup>) 466 (12 %, C<sub>27</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>3</sub><sup>+</sup>) 279 (100 %, C<sub>19</sub>H<sub>19</sub>O<sub>2</sub><sup>+</sup>); HRMS (C<sub>29</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>4</sub>) calcd. 498.18922, found 498.189495; Anal. Calcd. For C<sub>28</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>4</sub>: C, 67.60; H, 5.27; N, 2.82; found: C, 67.68; H, 5.29; N, 2.79%.

**methyl 2-((1*R*\*,2*R*\*)-2-((*S*\*)-phenyl(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)methyl)-2,3-dihydro-1*H*-inden-1-yl)acetate (470b)**



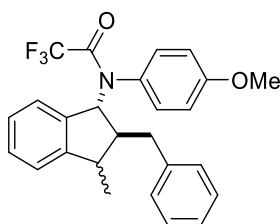
Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ea** (0.50 g, 0.92 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **470** as a mixture of diastereoisomers, further recrystallisation (CH<sub>2</sub>Cl<sub>2</sub>/hexanes) afforded **470b** as a white solid (49.8 mg, 0.10 mmol, 11 %); mp 157 – 158 °C; IR  $\nu_{\text{max}}$  (thin film) 2951 (C-H) 1735 (C=O, ester) 1687 (C=O, amide) 1510 (C=C, Ar) 1183, 1168 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.31 (1H, dd,  $J$  = 14.7, 3.9, CH<sub>2</sub>CO<sub>2</sub>Me) 2.38 (1H, dd,  $J$  = 14.5, 11.5, CH<sub>2</sub>CO<sub>2</sub>Me) 3.18 – 3.23 (2H, m, CHCHN & CH<sub>2</sub>Ar) 3.30 (1H, apt dd,  $J$  = 15.1, 12.6, CH<sub>2</sub>Ar) 3.40 (1H, ddd,  $J$  = 11.2, 6.7, 4.5, CHCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>) 3.48 (3H, s, OCH<sub>3</sub>) 3.76 (3H, s, OCH<sub>3</sub>) 5.84 (1H, br s, PMP-*H*) 6.30 (1H, br d,  $J$  = 6.9, CHN) 6.48 (1H, br d,  $J$  = 5.0, PMP-*H*) 6.83 (1H, dd,  $J$  = 8.8, 2.9, PMP-*H*) 6.99 – 7.15 (4H, m, Ar*H*) 7.21 – 7.34 (6H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  34.5 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>) 35.1 (ArCH<sub>2</sub>) 42.5 (CHCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>) 43.5 (CHCHN) 51.5 (CO<sub>2</sub>CH<sub>3</sub>) 55.5 (ArOCH<sub>3</sub>) 61.3 (CHN) 113.5 (2C, PMP-*C*) 116.8 (q,  $J$  = 289.0, CF<sub>3</sub>) 124.9 (ArC) 124.9 (2C, ArC) 126.5 (ArC) 126.7 (ArC) 127.5 (PMP-*C*) 128.8 (ArC) 129.1 (2C, ArC) 129.6 (q) 130.6 (ArC) 133.1 (PMP-*C*) 135.9 (q) 141.5 (q) 145.9 (q) 157.5 (q,  $J$  = 35.4, COCF<sub>3</sub>) 160.0 (q, ArCOCH<sub>3</sub>) 172.4 (q, CO<sub>2</sub>CH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 66.9 (3F, s, CF<sub>3</sub>); m/z (EI) 497 (100 %, M<sup>+</sup>) 466 (25 %, C<sub>27</sub>H<sub>23</sub>F<sub>3</sub>NO<sub>3</sub><sup>+</sup>) 428 (8 %, C<sub>27</sub>H<sub>26</sub>NO<sub>4</sub><sup>+</sup>) 400 (7 %, C<sub>26</sub>H<sub>26</sub>NO<sub>3</sub><sup>+</sup>) 279 (10 %, C<sub>19</sub>H<sub>19</sub>O<sub>2</sub><sup>+</sup>); HRMS (C<sub>28</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>4</sub>) calcd. 497.18139, found 497.181034.

***N*-(((1*R*\*,2*R*\*)-1-benzyl-2,3-dihydro-1*H*-inden-2-yl)(phenyl)methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**471a**)**



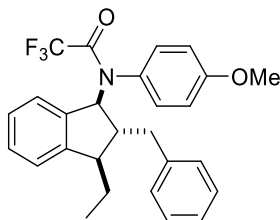
Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ga** (450 mg, 0.80 mmol). Purification by flash column chromatography (0 - 8 % Et<sub>2</sub>O/Hexanes) followed by recrystallisation (CH<sub>2</sub>Cl<sub>2</sub>/Hexanes) afforded **471a** as a single diastereomer as a white solid (11.0 mg, 0.021 mmol, 3 %); mp 162 – 164 °C; IR  $\nu_{\text{max}}$  (thin film) 2934 (C-H) 1684 (C=O, amide) 1584, 1510, 1454 (C=C, Ar) 1181, 1148 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.39 (1H, apt t,  $J$  = 12.3, PhCH<sub>2</sub>CH) 2.77 (1H, dd,  $J$  = 12.6, 3.4, PhCH<sub>2</sub>CH) 3.03 (1H, ddd,  $J$  = 11.2, 6.6, 3.4, BnCHAr) 3.17 – 3.25 (2H, m, CHCHN & ArCH<sub>2</sub>CHCHN) 3.38 (1H, m, ArCH<sub>2</sub>CHCHN) 3.77 (3H, s, OCH<sub>3</sub>) 5.95 (1H, br s, PMP-*H*) 6.10 (1H, d,  $J$  = 7.5, Ar*H*) 6.46 – 6.59 (4H, m, CHN, Ar*H*, 2 x PMP-*H*) 6.84 (1H, dd,  $J$  = 8.8, 3.0, PMP-*H*) 6.87 (1H, t,  $J$  = 7.5, Ar*H*) 7.06 – 7.12 (4H, m, Ar*H*) 7.16 (2H, dt,  $J$  = 7.5, 0.7, Ar*H*) 7.25 – 7.28 (1H, m, Ar*H*) 7.30 – 7.36 (3H, m, Ar*H*) 7.39 (1H, tm,  $J$  = 7.3, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  35.2 (ArCH<sub>2</sub>) 35.2 (ArCH<sub>2</sub>) 44.2 (CHCHN) 48.7 (CHCHCHN) 55.5 (OCH<sub>3</sub>) 61.6 (CHN) 113.4 (2C, PMP-C) 116.8 (q,  $J$  = 288.8, CF<sub>3</sub>) 124.6 (ArC) 125.5 (2C, ArC) 125.5 (ArC) 126.0 (ArC) 126.9 (PMP-C) 128.0 (2C, ArC) 128.7 (2C, ArC) 128.9 (ArC) 129.6 (3C, ArC) 129.8 (q, ArCN) 130.8 (ArC) 133.2 (PMP-C) 136.5 (q, ArCCHN) 139.9 (q, ArCCH<sub>2</sub>) 141.6 (q, ArCCH<sub>2</sub>CHCHN) 146.0 (q, ArCCH) 157.5 (q,  $J$  = 35.4, COCF<sub>3</sub>) 160.0 (ArCOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 66.8 (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 538 (100 %, M + Na<sup>+</sup>) 516 (100 %, M + H<sup>+</sup>); HRMS (C<sub>32</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 516.2150, found 516.2166.

***N*-(2-benzyl-3-methyl-2,3-dihydro-1*H*-inden-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (437)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ad** (0.48 g, 0.99 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **437** as a 1.3:1 mixture of inseparable diastereomers as a colourless oil (200 mg, 0.46 mmol, 46 %); IR  $\nu_{\text{max}}$  (thin film) 1686 (C=O, amide) 1510 (C=C, Ar) 1186, 1153 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{trans,trans}}$  0.97 (3H, d,  $J$  = 7.0, CHCH<sub>3</sub>) 1.99 (1H, tdd,  $J$  = 8.7, 7.6, 6.1, CHCHN) 2.85 (1H, m, CHCH<sub>3</sub>) 2.95 (1H, dd,  $J$  = 13.7, 6.0, CH<sub>2</sub>Ph) 3.03 (1H, dd,  $J$  = 13.7, 7.5, CH<sub>2</sub>Ph) 3.76 (3H, s, OCH<sub>3</sub>) 6.28 (1H, d,  $J$  = 8.8, CHN) 6.37 (1H, apt d,  $J$  = 8.6, PMP-*H*) 6.59 (1H, dd,  $J$  = 8.9, 2.9, PMP-*H*) 6.61 – 6.65 (1H, m, PMP-*H*) 6.76 (1H, dd,  $J$  = 8.8, 2.9, PMP-*H*) 7.09 – 7.13 (2H, m, Ar*H*) 7.23 – 7.39 (7H, m, Ar*H*)  $\delta_{\text{trans,cis}}$  1.12 (3H, d,  $J$  = 7.3, CH<sub>3</sub>) 2.60 (1H, tdd,  $J$  = 9.2, 7.9, 6.7, CHCHN) 2.90 (1H, dd,  $J$  = 14.5, 9.2, CH<sub>2</sub>Ph) 2.96 – 3.04 (2H, m, CH<sub>2</sub>Ph & CHCHCHN) 3.77 (3H, s, OCH<sub>3</sub>) 6.24 (1H, d,  $J$  = 9.2, CHN) 6.61 – 6.65 (1H, m, PMP-*H*) 6.70 (1H, dm,  $J$  = 8.7, PMP-*H*) 6.83 (2H, m, PMP-*H*) 7.18 (2H, apt d,  $J$  = 7.5, Ar*H*) 7.23 – 7.39 (7H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta_{\text{trans,trans}}$  18.8 (CH<sub>3</sub>CH) 39.2 (CH<sub>2</sub>) 42.6 (CH<sub>3</sub>CH) 51.4 (CHCHN) 55.4 (OCH<sub>3</sub>) 67.0 (CHN) 113.6 – 132.1 (ArC & PMP-C) 116.6 (q,  $J$  = 288.3, CF<sub>3</sub>) 127.9 (q, ArCN) 139.6 (q, ArCCHN) 139.6 (q, ArCCH<sub>2</sub>) 146.7 (q, ArCCHCH<sub>3</sub>) 158.2 (q,  $J$  = 35.1, CF<sub>3</sub>CO) 159.8 (q, ArCO)  $\delta_{\text{trans,cis}}$  17.3 (CH<sub>3</sub>CH) 34.4 (CH<sub>2</sub>) 39.3 (CH<sub>3</sub>CH) 45.3 (CHCHN) 55.5 (OCH<sub>3</sub>) 66.3 (CHN) 113.6 – 132.1 (ArC & PMP-C) 116.6 (q,  $J$  = 289.2, CF<sub>3</sub>) 127.8 (q, ArCN) 139.1 (q, ArC) 140.0 (q, ArC) 148.7 (q, ArCCHCH<sub>3</sub>) 158.5 (q,  $J$  = 34.6, CF<sub>3</sub>CO) 160.0 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta_{\text{trans,trans}}$  – 66.9 ppm (3F, s, CF<sub>3</sub>)  $\delta_{\text{trans,cis}}$  – 66.8 ppm (3F, s, CF<sub>3</sub>);  $m/z$  (EI) 439 (6 %, M<sup>+</sup>) 221 (100 %, C<sub>17</sub>H<sub>17</sub><sup>+</sup>) 91 (98 %, C<sub>7</sub>H<sub>7</sub><sup>+</sup>); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 439.17591, found 439.176345.

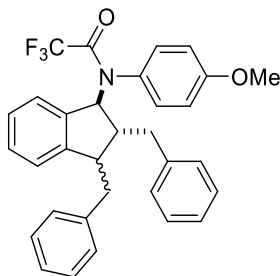
***N*-((1*S*\*,2*R*\*,3*R*\*)-2-benzyl-3-ethyl-2,3-dihydro-1*H*-inden-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**478a**)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ao** (134 mg, 0.27 mmol). Purification via flash column chromatography (0 – 10 % Et<sub>2</sub>O/hexanes) afforded **478a** as a mixture of diastereoisomers (70:30) as a colourless oil (14.7 mg, 0.032 mmol, 12 %); IR  $\nu_{\text{max}}$  (thin film) 2958, 2928, 2857 (C-H) 1688 (C=O, amide) 1510, 1454 (C=C, Ar) 1187, 1150 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{trans,trans}}$  0.44 (3H, s, CH<sub>2</sub>CH<sub>3</sub>) 1.29 (1H, m, CH<sub>2</sub>CH<sub>3</sub>) 1.41 (1H, m, CH<sub>2</sub>CH<sub>3</sub>) 2.22 (1H, apt quint, *J* = 7.3, CHCHN) 2.86 (1H, m, CHEt) 2.93 (2H, d, *J* = 7.1, CH<sub>2</sub>Ph) 3.73 (3H, s, OCH<sub>3</sub>) 6.25 (1H, dd, *J* = 8.7, 1.1, PMP-*H*) 6.30 (1H, d, *J* = 7.6, CHN) 6.48 (1H, dd, *J* = 8.8, 2.6, PMP-*H*) 6.53 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 6.72 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 7.09 (1H, m, Ar*H*) 7.24 – 7.30 (5H, m, Ar*H*) 7.32 – 7.37 (3H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta_{\text{trans,trans}}$  9.76 (CH<sub>2</sub>CH<sub>3</sub>) 25.1 (CH<sub>2</sub>CH<sub>3</sub>) 40.8 (PhCH<sub>2</sub>) 46.4 (CHCHN) 49.0 (CHEt) 55.5 (OCH<sub>3</sub>) 67.3 (CHN) 113.5 (PMP-C) 113.7 (PMP-C) 116.6 (q, *J* = 288.2, CF<sub>3</sub>) 124.2 (ArC) 124.5 (ArC) 126.7 (ArC) 127.2 (ArC) 127.9 (q, ArCN) 128.5 (ArC) 128.6 (2C, ArC) 129.4 (2C, ArC) 130.5 (PMP-C) 132.2 (PMP-C) 139.9 (q, ArCCH<sub>2</sub>) 140.3 (q, ArCCHN) 145.5 (q, ArCCHEt) 157.8 (q, *J* = 34.9, COCF<sub>3</sub>) 159.8 (ArCOCH<sub>3</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  - 67.0 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 929 (47 %, 2M + H + Na<sup>+</sup>) 476 (100 %, M + H<sup>+</sup>) 235 (30 %, C<sub>18</sub>H<sub>19</sub><sup>+</sup>); HRMS (C<sub>27</sub>H<sub>26</sub>NO<sub>2</sub>F<sub>3</sub>Na) calcd. 476.1808, found 476.1808.



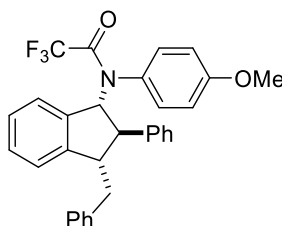
***N*-(2,3-dibenzyl-2,3-dihydro-1*H*-inden-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (477)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ag** (558 mg, 1.00 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **477** as two diastereomers (60:40) as a colourless oil (174 mg, 0.34 mmol, 34 %); IR  $\nu_{\text{max}}$  (thin film) 3063, 3026, 2934 (C-H) 1689 (C=O, amide) 1584, 1511 (C=C, Ar) 1186, 1170 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta_{\text{trans,trans}}$  2.21 (1H, dtd,  $J = 9.6, 7.1, 4.8$  CHNCH) 2.24 (1H, dd,  $J = 13.4, 8.2$ , CHNCHCHCH<sub>2</sub>) 2.51 (1H, dd,  $J = 13.3, 4.6$ , CHNCHCHCH<sub>2</sub>) 2.70 (1H, dd,  $J = 13.4, 9.6$ , CHNCHCHCH<sub>2</sub>) 2.79 (1H, dd,  $J = 13.6, 6.3$ , CHNCHCHCH<sub>2</sub>) 3.13 – 3.18 (1H, m, CHNCHCH) 3.78 (3H, s, OCH<sub>3</sub>) 6.17 (1H, d,  $J = 7.8$ , PMP-*H*) 6.31 (1H, d,  $J = 7.1$ , CHN) 6.42 (1H, dd,  $J = 8.7, 2.6$ , PMP-*H*) 6.54 (1H, dd,  $J = 8.9, 3.0$ , PMP-*H*) 6.75 (1H, dd,  $J = 8.8, 3.0$ , PMP-*H*) 6.91 (2H, m, Ar*H*) 7.05 (3H, apt d,  $J = 7.0$ , Ar*H*) 7.15 – 7.35 (8H, m, Ar*H*) 7.37 (1H, d,  $J = 7.4$ , Ar*H*)  $\delta_{\text{trans,cis}}$  2.44 (1H, dd,  $J = 13.4, 8.2$ , CHNCHCHCH<sub>2</sub>) 2.69 (1H, m, CHNCH) 3.05 (2H, m, CHNCHCH<sub>2</sub>) 3.10 (1H, ddd,  $J = 10.8, 7.5, 5.0$ , CHNCHCH) 3.13 – 3.18 (1H, m, CHNCHCHCH<sub>2</sub>) 3.78 (3H, s, OCH<sub>3</sub>) 6.24 (1H, d,  $J = 7.3$ , Ar*H*) 6.28 (1H, d,  $J = 9.2$ , CHN) 6.63 (1H, dd,  $J = 8.9, 2.9$ , PMP-*H*) 6.69 (1H, dd,  $J = 8.9, 2.5$ , PMP-*H*) 6.78 (2H, m, Ar*H*) 6.86 (1H, dd,  $J = 8.8, 2.9$ , PMP-*H*) 6.95 (1H, m, PMP-*H*) 7.00 (1H, apt t,  $J = 7.4$ , Ar*H*) 7.15 – 7.35 (9H, m, Ar*H*) 7.40 (1H, d,  $J = 7.6$ , Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta_{\text{trans,trans}}$  41.0 (CH<sub>2</sub>CHCHN) 41.2 (CH<sub>2</sub>CHCHCHN) 47.5 (CHCHN) 49.8 (CHCHCHN) 55.5 (OCH<sub>3</sub>) 67.3 (CHN) 113.5 (PMP-C) 113.7 (PMP-C) 116.6 (q,  $J = 288.7$ , CF<sub>3</sub>) 124.5 – 129.4 (14C, ArC, indistinguishable) 128.0 (q, ArCN) 130.3 (PMP-C) 132.3 (PMP-C) 139.3 (q, ArCCH<sub>2</sub>CHCHCHN) 139.6 (q, ArCCH<sub>2</sub>CHCHN) 140.2 (ArCCHN) 145.6 (q, ArCCHCHCHN) 157.6 (q,  $J = 34.8$ , COCF<sub>3</sub>) 159.8 (q, ArCO)  $\delta_{\text{trans,cis}}$  34.1 (CH<sub>2</sub>CHCHN) 36.5 (CH<sub>2</sub>CHCHCHN) 46.0 (CHCHN) 46.2 (CHCHCHN) 55.5 (OCH<sub>3</sub>) 66.0 (CHN) 113.9 (PMP-C) 114.0 (PMP-C) 116.7 (q,  $J = 289.4$ , CF<sub>3</sub>) 124.5 – 129.4 (14C, ArC, indistinguishable) 127.8 (q, ArCN) 130.8 (PMP-C) 131.6 (PMP-C) 139.5 (q,

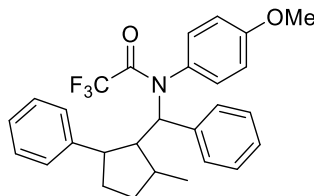
ArCCH<sub>2</sub>CHCHN) 139.6 (q, ArCCHN) 139.8 (q, ArCCH<sub>2</sub>CHCHCHN) 145.7 (q, ArCCHCHCHN) 158.6 (q,  $J = 34.7$ , COCF<sub>3</sub>) 160.1 (q, ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta_{\text{trans,trans}} - 67.0$  ppm (3F, s, CF<sub>3</sub>)  $\delta_{\text{trans,cis}} - 66.8$  ppm (3F, s, CF<sub>3</sub>); m/z (ESI<sup>+</sup>) 533 (37 %, M + NH<sub>4</sub><sup>+</sup>) 516 (48 %, M + H<sup>+</sup>); HRMS (C<sub>32</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 516.2150, found 516.2152.

***N*-((1*R*\*,2*R*\*,3*S*\*)-3-benzyl-2-phenyl-2,3-dihydro-1*H*-inden-1-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**509**)**

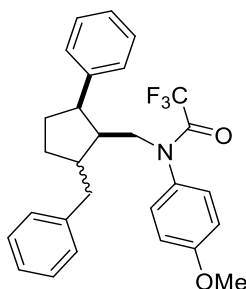


Prepared by *general procedure I* using nitro compound **352ag** (253 mg, 0.46 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **509** as a mixture of diastereoisomers (95:5) as a colourless oil (30.0 mg, 0.06 mmol, 13 %); IR  $\nu_{\text{max}}$  (thin film) 2920, 2836 (C-H) 1689 (C=O, amide) 1603, 1509, 1453 (C=C, Ar) 1147, 1109 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.67 (1H, dd,  $J = 14.5, 7.9$ , CH<sub>2</sub>Ar) 2.85 (1H, dd,  $J = 14.5, 5.0$ , CH<sub>2</sub>Ar) 3.02 (1H, t,  $J = 9.2$ , CHCH<sub>2</sub>Ar) 3.53 (1H, m, CHCHN) 3.81 (3H, s, OCH<sub>3</sub>) 6.48 (1H, d,  $J = 9.4$ , CHN) 6.61 (1H, dd,  $J = 8.8, 2.6$ , PMP-*H*) 6.65 (1H, apt d,  $J = 8.9$ , PMP-*H*) 6.84 (1H, dd,  $J = 8.7, 2.6$ , PMP-*H*) 6.90 – 6.94 (3H, m, Ar*H*) 7.01 (1H, d,  $J = 7.6$ , Ar*H*) 7.09 – 7.18 (5H, m, PMP-*H* & Ar*H*) 7.24 – 7.28 (2H, m, Ar*H*) 7.30 – 7.35 (3H, m, Ar*H*) 7.38 (1H, d,  $J = 7.6$ , Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  38.5 (CH<sub>2</sub>Ar) 51.9 (CHCHN) 53.7 (CHCH<sub>2</sub>Ar) 55.5 (OCH<sub>3</sub>) 68.8 (CHN) 113.7 (PMP-*C*) 114.1 (PMP-*C*) 116.6 (q,  $J = 288.5$ , CF<sub>3</sub>) 124.0 (Ar*C*) 124.6 (Ar*C*) 126.1 (Ar*C*) 127.2 (Ar*C*) 127.6 (2*C*, Ar*C*) 128.0 (q, ArCN) 128.3 (2*C*, Ar*C*) 128.5 (2*C*, Ar*C*) 128.5 (Ar*C*) 128.9 (Ar*C*) 129.3 (2*C*, Ar*C*) 130.6 (PMP-*C*) 132.2 (PMP-*C*) 139.3 (q, ArCCH<sub>2</sub>) 139.7 (q, ArCCHN) 140.8 (q, ArCCHCHN) 144.5 (q, ArCCHCHCHN) 158.2 (q,  $J = 35.2$ , COCF<sub>3</sub>) 160.0 (ArCO); <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta - 67.0$  ppm (3F, s, CF<sub>3</sub>); m/z (EI) 501.2 (2 %, M<sup>+</sup>) 283.2 (59 %, C<sub>22</sub>H<sub>19</sub><sup>+</sup>); HRMS (C<sub>31</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 501.19102, found 501.190981.

## 3.3.11.2 Formation of cyclopropanes

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((2-methyl-5-phenylcyclopentyl)(phenyl)methyl)acetamide (492)**

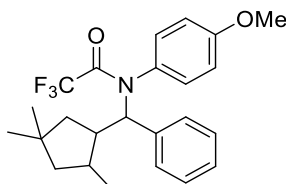
Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ra** (87.0 mg, 0.17 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **492** as a mixture of diastereoisomers as white solid (19.0 mg, 0.041 mmol, 24 %); IR  $\nu_{\max}$  (thin film) 2960, 2932 (C-H) 1689 (C=O, amide) 1511, 1445 (C=C, Ar) 1204, 1184 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data display a complex mixture; *m/z* (EI) 935 (8 %, 2M<sup>+</sup>) 468 (100 %, M<sup>+</sup>); HRMS (C<sub>28</sub>H<sub>28</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 468.2152, found 468.2150.

***N*-(((1*S*\*,5*R*\*)-2-benzyl-5-phenylcyclopentyl)methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (493)**

Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102ra** (87.0 mg, 0.17 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **493** as a white solid (2.5 mg, 0.003 mmol, 3 %); IR  $\nu_{\max}$  (thin film) 3027, 2954, 2935 (C-H) 1692 (C=O, amide) 1602, 1511, 1445 (C=C, Ar) 1202, 1152 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.54 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CHPh) 1.61 (1H, m, CH<sub>2</sub>CHPh) 1.74 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CHPh) 2.25 -2.33 (2H, m, 1H, m, CH<sub>2</sub>CHPh & CHCH<sub>2</sub>N) 2.40 – 2.47 (2H, m, CH<sub>2</sub>Ph & CHCH<sub>2</sub>Ph) 2.77 (1H, m, CH<sub>2</sub>Ph) 3.13 (1H, dt, *J* = 9.0, 8.2, CHPh) 3.62 (1H, dd, *J* = 13.5, 6.0, CH<sub>2</sub>N) 3.79 (3H, s, OCH<sub>3</sub>) 4.28 (1H, dd, *J* = 13.4, 9.1, CH<sub>2</sub>N) 6.84 – 7.55 (14 H, m, ArH & PMP-H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  30.8 (CH<sub>2</sub>) 34.7 (CH<sub>2</sub>CHPh) 35.6 (CH<sub>2</sub>Ph) 43.9 (CHCH<sub>2</sub>Ph) 47.6 (CHCH<sub>2</sub>N) 49.0 (CHPh) 52.6 (CH<sub>2</sub>N) 55.5 (OCH<sub>3</sub>) 126.0 (ArC) 126.4 (ArC) 127.5 (ArC) 128.5 (ArC) 128.7 (ArC) 128.9 (ArC)

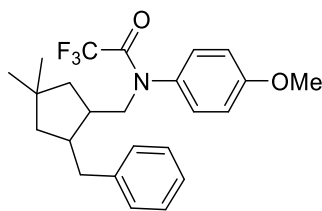
131.0 (q, ArCN) 141.2 (q, ArC) 146.5 (q, ArC) 157.6 (q,  $J = 34.4$ , CF<sub>3</sub>) 159.5 (ArCO) further signals indistinguishable; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.0 ppm (3F, s, CF<sub>3</sub>);  $m/z$  (ES<sup>+</sup>) 935 (16 %, 2M + H<sup>+</sup>) 468 (100 %, M + H<sup>+</sup>); HRMS (C<sub>28</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 468.2150, found 468.2154.

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(phenyl(2,4,4-trimethylcyclopentyl)methyl)acetamide (490)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102qa** (257 mg, 0.55 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **490** as a mixture of diastereoisomers (40:30:30) as a white solid (52.6 mg, 0.13 mmol, 46 %); IR  $\nu_{\max}$  (thin film) 3031, 2450, 2862 (C-H) 1685 (C=O, amide) 1606, 1582, 1509 (C=C, Ar) 1179, 1146 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data display a complex mixture;  $m/z$  (ESI<sup>+</sup>) 839 (23 %, 2M + H<sup>+</sup>) 461 (9 %, M + MeCN + H<sup>+</sup>) 420 (100 %, M + H<sup>+</sup>); HRMS (C<sub>24</sub>H<sub>29</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 420.2150, found 420.2153.

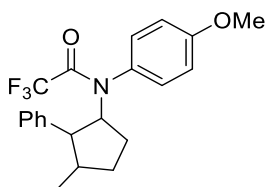
***N*-((1-benzyl-2,3-dihydro-1H-inden-2-yl)methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (491)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102qa** (257 mg, 0.55 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **491** as a white solid (19.6 mg, 0.047 mmol, 9 %); mp 109 – 111 °C; IR  $\nu_{\max}$  (thin film) 2951 2933 2865 (C-H) 1697 (C=O, amide) 1512 (C=C, Ar) 1202, 1151 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  0.92 (3H, s, CH<sub>3</sub>) 1.11 (3H, s, CH<sub>3</sub>) 1.34 (1H, dd,  $J = 13.0$ , 8.5, CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>) 1.40 (1H, dd,  $J = 13.0$ , 6.6, CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>) 1.50 (1H, dd,  $J = 13.0$ , 7.8, CH<sub>2</sub>CHCH<sub>2</sub>N) 1.58 (1H, dd,  $J = 13.0$ , 7.3, CH<sub>2</sub>CHCH<sub>2</sub>N) 2.27 (1H, m, CHCH<sub>2</sub>N) 2.38 (1H, m, CHCH<sub>2</sub>Ph) 2.43 (1H, dd,  $J = 12.8$ , 10.7, CH<sub>2</sub>Ph) 2.70 (1H, dd,  $J = 12.8$ , 4.7,

$\text{CH}_2\text{Ph}$ ) 3.49 (1H, dd,  $J = 13.1, 4.9$ ,  $\text{CH}_2\text{N}$ ) 3.85 (3H, s,  $\text{OCH}_3$ ) 4.25 (1H, dd,  $J = 13.0, 11.0$ ,  $\text{CH}_2\text{N}$ ) 6.91 (2H, apt d,  $J = 8.7$ , PMP- $H$ ) 7.08 (2H, apt d,  $J = 7.8$ , Ar $H$ ) 7.11 (2H, d,  $J = 8.6$ , PMP- $H$ ) 7.16 (1H, tm,  $J = 7.4$ , Ar $H$ ) 7.22 – 7.25 (2H, m, Ar $H$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  30.6 ( $\text{C}(\text{CH}_3)_2$ ) 31.4 ( $\text{C}(\text{CH}_3)_2$ ) 36.5 ( $\text{CH}_2\text{Ph}$ ) 37.4 (q,  $\text{C}(\text{CH}_3)_2$ ) 38.8 ( $\text{CHCH}_2\text{N}$ ) 42.4 ( $\text{CHCH}_2\text{Ph}$ ) 44.7 ( $\text{CH}_2\text{CHCH}_2\text{N}$ ) 46.3 ( $\text{CH}_2\text{CHCH}_2\text{Ph}$ ) 52.4 ( $\text{CH}_2\text{N}$ ) 55.6 ( $\text{OCH}_3$ ) 114.0 (PMP-C) 114.7 (PMP-C) 116.7 (q,  $J = 288.8$ ,  $\text{CF}_3$ ) 125.9 (ArC) 128.4 (2C, ArC) 128.8 (2C, ArC) 129.4 (br, PMP-C) 130.0 (br, PMP-C) 131.2 (ArCN) 141.4 (q,  $\text{ArCCH}_2$ ) 157.5 (q,  $J = 34.8$ ,  $\text{COCF}_3$ ) 159.8 (q,  $\text{ArCOCH}_3$ );  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  – 66.9 ppm (3F, s,  $\text{CF}_3$ );  $m/z$  ( $\text{ESI}^+$ ) 839 (27 %,  $2\text{M} + \text{H}^+$ ) 420 (100 %,  $\text{M} + \text{H}^+$ ); HRMS ( $\text{C}_{24}\text{H}_{29}\text{F}_3\text{NO}_2$ ) calcd. 420.2150, found 420.2152.

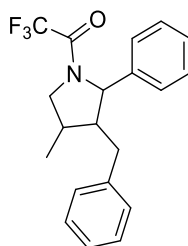
**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-(3-methyl-2-phenylcyclopentyl)acetamide (508)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **352ac** (0.42 g, 1.00 mmol). Purification by flash column chromatography (10 %  $\text{Et}_2\text{O}$ /Hexanes) afforded **508** as a mixture of inseparable diastereomers (50:50) as a colourless oil (134 mg, < 0.36 mmol, < 36 %); IR  $\nu_{\text{max}}$  (thin film) 2954, 2914 (C-H) 1684 (C=O, amide) 1509, 1453 (C=C, Ar) 1187, 1149 (C-F,  $\text{CF}_3$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data display a complex mixture;  $m/z$  ( $\text{CI}^+$ ) 772 (100 %,  $2\text{M} + \text{CH}_5^+$ ) 755 (99 %,  $2\text{M} + \text{H}^+$ ) 395 (100 %,  $\text{M} + \text{CH}_5^+$ ) 378 (90 %,  $\text{M} + \text{H}^+$ ); HRMS ( $\text{C}_{21}\text{H}_{22}\text{F}_3\text{NO}_2$ ) calcd. 378.16754, found 378.167530.

### 3.3.11.3 Formation of pyrrolidines

#### 1-(3-benzyl-4-methyl-2-phenylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (494)

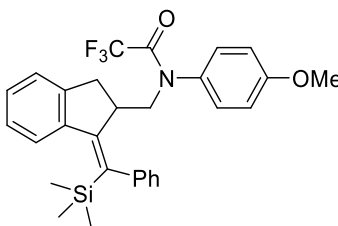


Prepared by *general procedure I* using nitro compound **102at** (150 mg, 0.38 mmol). Purification by flash column chromatography (10 % Et<sub>2</sub>O/Hexanes) afforded **494** as a mixture of diastereoisomers (50:30:15:5) as a colourless oil (16.3 mg, 0.05 mmol, 12 %); IR  $\nu_{\text{max}}$  (thin film) 3059, 3026, 2918, 2847 (C-H) 1686 (C=O, amide) 1601, 1493, 1451 (C=C, Ar) 1196, 1135 (C-F, CF<sub>3</sub>); <sup>1</sup>H and <sup>13</sup>C NMR data display a complex mixture; m/z (ESI) 717 (100 %, 2M + Na<sup>+</sup>) 370 (63 %, M + Na<sup>+</sup>) 348 (100 %, M + H<sup>+</sup>); HRMS (C<sub>20</sub>H<sub>21</sub>F<sub>3</sub>NO) calcd. 348.1570, found 348.1575.

### 3.3.12 Intramolecular addition to an alkyne

#### 3.3.12.1 Formation of *exo*-methylene indanes

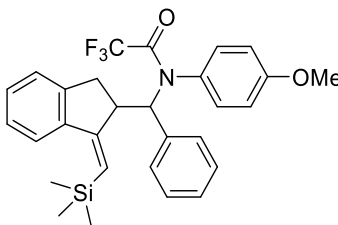
##### (*Z*)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1-(phenyl(trimethylsilyl)methylene)-2,3-dihydro-1*H*-inden-2-yl)methyl)acetamide (**518**)



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102va** (556 g, 1.00 mmol). Purification by flash column chromatography (0 - 10 % Et<sub>2</sub>O/Hexanes) followed by recrystallisation (PhMe/Hexanes) afforded **518** as a white solid (30.0 mg, 0.59 mmol, 6 % yield); mp 144 – 146 °C; IR  $\nu_{\text{max}}$  (thin film) 3056, 2956, 2092, 2840 (C-H) 1696 (C=O, amide) 1511 (C=C, Ar) 1201, 1153 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  0.07 (9H, s, Si(CH<sub>3</sub>)<sub>3</sub>) 2.72 (1H, apt d, *J* = 15.4, ArCH<sub>2</sub>) 2.90 (1H, dd, *J* = 13.3, 3.3, CH<sub>2</sub>N) 2.93 – 3.03 (2H, m, CHCH<sub>2</sub>N & ArCH<sub>2</sub>) 3.85 (3H, s, OCH<sub>3</sub>) 4.01 (1H, dd, *J* = 13.1, 11.5, CH<sub>2</sub>N) 6.60 – 7.17 (9H, br m, ArH & PMP-H) 7.24 (1H, apt t, *J* = 7.4, ArH) 7.28 (1H,

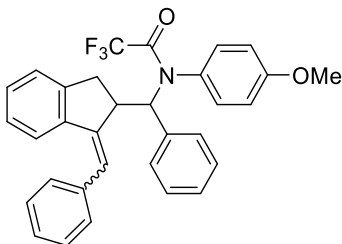
dd,  $J = 7.2, 1.0$ , ArH) 7.32 (1H, d,  $J = 7.3$ , ArH) 7.66 (1H, d,  $J = 7.5$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  0.5 ( $\text{Si}(\text{CH}_3)_3$ ) 33.5 (ArCH<sub>2</sub>) 42.1 (CHCH<sub>2</sub>N) 52.3 (CH<sub>2</sub>N) 55.6 (OCH<sub>3</sub>) 116.5 (q,  $J = 288.9$ , CF<sub>3</sub>) 125.2 (ArC) 125.5 (1C, ArC) 126.0 (1C, ArC) 126.3 (1C, ArC) 127.4 (br, ArC) 128.8 (ArC) 130.0 (q, ArCN) 139.4 (q, CSiMe<sub>3</sub>) 139.8 (q, ArCCH<sub>2</sub>) 145.2 (ArCCSiMe<sub>3</sub>) 146.6 (ArCCCSiMe<sub>3</sub>) 153.5 (CCSiMe<sub>3</sub>) 157.6 (q,  $J = 35.4$ , COCF<sub>3</sub>) 159.3 (q, ArCO);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  - 67.0 ppm (3F, s, CF<sub>3</sub>);  $m/z$  ( $\text{CI}^+$ ) 527 (46 %,  $\text{M} + \text{NH}_4^+$ ) 510 (100 %,  $\text{M} + \text{H}^+$ ) 291 (6 %,  $\text{C}_{20}\text{H}_{23}\text{Si}^+$ ); HRMS ( $\text{C}_{29}\text{H}_{31}\text{F}_3\text{NO}_2\text{Si}$ ) calcd. 510.2071, found 510.2070. Anal. Calcd. For  $\text{C}_{29}\text{H}_{30}\text{F}_3\text{NO}_2\text{Si}$ : C, 68.35; H, 5.93; N, 2.75; found: C, 68.39; H, 5.91; N, 2.69 %.

**(Z)-2,2,2-trifluoro-N-(4-methoxyphenyl)-N-(phenyl(1-((trimethylsilyl)methylene)-2,3-dihydro-1H-inden-2-yl)methyl)acetamide (517)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102va** (556 mg, 1.00 mmol). Purification by flash column chromatography (0 - 10 % Et<sub>2</sub>O/Hexanes afforded **517** as a yellow oil (74.0 mg, 0.15 mmol, < 15 % yield); IR  $\nu_{\text{max}}$  (thin film) 2952 (C-H) 1690 (C=O, amide) 1606, 1583, 1509 (C=C, Ar) 1179, 1148 (C-F, CF<sub>3</sub>)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  0.29 (9H, s,  $\text{Si}(\text{CH}_3)_3$ ) 2.27 (1H, apt d,  $J = 16.7$ , CH<sub>2</sub>) 3.04 (1H, dd,  $J = 16.6, 7.5$ , CH<sub>2</sub>) 3.78 (3H, s, OCH<sub>3</sub>) 4.21 (1H, br dd,  $J = 10.8, 7.6$ , CHCHN) 4.55 (1H, br d,  $J = 10.8$ , CHN) 5.99 (1H, s, CHSi) 6.67 (1H, dd,  $J = 8.9, 3.0$ , PMP-H) 6.71 – 6.74 (1H, m, PMP-H) 6.80 (1H, dd,  $J = 8.7, 2.7$ , PMP-H) 7.07 (1H, m, PMP-H) 7.11 (1H, d,  $J = 7.7$ , ArH) 7.18 – 7.31 (7H, m, ArH) 7.67 (1H, d,  $J = 7.5$ , ArH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  0.05 ( $\text{Si}(\text{CH}_3)_3$ ) 35.5 (CH<sub>2</sub>) 48.0 (CHCHN) 55.5 (OCH<sub>3</sub>) 71.1 (CHN) 113.5 (PMP-C) 114.3 (PMP-C) 124.6 (ArC) 124.8 (ArC) 125.7 (ArC) 126.6 (ArC) 128.3 (2C, ArC) 128.5 (2C, ArC) 128.7 (ArC) 130.1 (PMP-C) 130.4 (q, ArCN) 131.2 (PMP-C) 137.3 (q, ArC) 140.4 (q, ArC) 145.7 (q, ArCCH<sub>2</sub>) 156.9 (q,  $J = 35.5$ , COCF<sub>3</sub>) 159.3 (q, CCHSi) 159.6 (ArCO) further signals indistinguishable;  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz)  $\delta$  - 67.5 ppm (3F, s, CF<sub>3</sub>);  $m/z$  (EI) 509 (< 5 %,  $\text{M}^+$ ) 308 (100 %,  $\text{C}_{16}\text{H}_{13}\text{F}_3\text{NO}_2^+$ ) 202 (37 %,  $\text{C}_{13}\text{H}_{17}\text{Si}^+$ ).

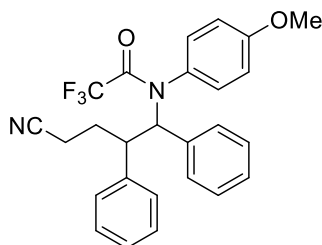
***N*-((1-benzylidene-2,3-dihydro-1*H*-inden-2-yl)(phenyl)methyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**519**)**



Prepared by *general procedure I* using  $\beta$ -nitroacetamide **102wa** (422 mg, 0.75 mmol). Purification by flash column chromatography (0 - 10 % Et<sub>2</sub>O/Hexanes afforded **519** followed by recrystallisation (Et<sub>2</sub>O/hexanes) as a white solid (40.3 mg, 0.078 mmol, < 10 % yield); mp 100 – 102 °C; IR  $\nu_{\text{max}}$  (thin film) 2956 (C-H) 1692 (C=O, amide) 1509 (C=C, Ar) 1185, 1150 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.85 (1H, m, CHCHN) 2.91 (1H, dd, *J* = 16.0, 7.5, CH<sub>2</sub>) 3.16 (1H, dd, *J* = 15.8, 8.0, CH<sub>2</sub>) 3.80 (3H, s, OCH<sub>3</sub>) 6.23 – 6.27 (2H, m, CHN & CH) 6.79 (1H, dd, *J* = 9.0, 2.7, PMP-*H*) 6.85 – 6.88 (2H, m, CH) 6.94 (1H, dd, *J* = 8.9, 2.7, PMP-*H*) 7.10 – 7.14 (2H, m, Ar*H*) 7.21 (1H, m, Ar*H*) 7.25 (1H, d, *J* = 7.4, Ar*H*) 7.28 – 7.58 (10H, m, Ar*H*); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.8 (CH<sub>2</sub>) 39.9 (CHCHN) 55.6 (OCH<sub>3</sub>) 64.4 (CHN) 113.6 (PMP-C) 114.5 (PMP-C) 124.4 (CCH) 130.7 (q) 131.8 (q) 138.1 (q) 138.4 (q) 139.0 (q) 139.8 (q) 146.0 (q) 158.9 (q, *J* = 35.2, COCF<sub>3</sub>) 160.1 (q, ArCO) further signals indistinguishable; *m/z* (ESI) 514 (100 %, *M* + *H*<sup>+</sup>) 295 (33 %, C<sub>23</sub>H<sub>19</sub><sup>+</sup>); HRMS (C<sub>32</sub>H<sub>27</sub>F<sub>3</sub>NO<sub>2</sub>) calcd. 514.1994, found 514.1999.

### 3.3.13 Intermolecular addition to an alkene

***N*-(4-cyano-1,2-diphenylbutyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (**543**)**



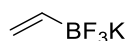
To a degassed solution of  $\beta$ -nitroacetamide **532aa** (89.5 mg, 0.20 mmol), AIBN (9.6 mg, 0.06 mmol, 0.3 eq) and acrylonitrile (135  $\mu$ L, 2.06 mmol, 10 eq) in benzene (4.5 mL) was added degassed Bu<sub>3</sub>SnH (270  $\mu$ L, 1.01 mmol, 5 eq) via syringe pump over 3 h, the



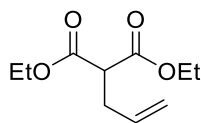
reaction was stirred for 24 h and concentrated *in vacuo*. The crude mixture was partitioned between MeCN/Hexanes and the MeCN layer was concentrated *in vacuo*. Purification by flash column chromatography (0 – 20 % Et<sub>2</sub>O/hexanes) afforded **543** as a colourless oil (22.7 mg, 0.050 mmol, 25 %); IR  $\nu_{\text{max}}$  (thin film) 2955, 2924, 2850 (C-H) 2245 (C-N, nitrile) 1690 (C=O, amide) 1509 (C=C, Ar) 1181 (C-F, CF<sub>3</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  1.58 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CN) 1.85 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CN) 1.94 (1H, ddd, *J* = 16.8, 9.6, 7.2, CH<sub>2</sub>CH<sub>2</sub>CN) 2.09 (1H, ddd, *J* = 16.8, 7.2, 4.5, CH<sub>2</sub>CH<sub>2</sub>CN) 3.64 (1H, br s, CHCHN) 3.79 (3H, s, OCH<sub>3</sub>) 5.86 (1H, dd, *J* = 8.8, 2.2, PMP-*H*) 5.94 (1H, br s, CHN) 6.55 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 6.60 (1H, dd, *J* = 8.7, 2.1, PMP-*H*) 6.74 (1H, dd, *J* = 8.8, 2.9, PMP-*H*) 7.29 – 7.44 (8H, m, ArH) 7.47 (2H, d, *J* = 7.4, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  15.1 (CH<sub>2</sub>CN) 30.4 (CH<sub>2</sub>CH<sub>2</sub>CN) 44.7 (CHCHN) 55.5 (OCH<sub>3</sub>) 113.3 (PMP-C) 113.6 (PMP-C) 116.3 (q, *J* = 289.7, CF<sub>3</sub>) 119.2 (q, CN) 128.2 (2C, ArC) 128.4 (br q, ArCN) 129.0 (4C, ArC) 129.1 (2C, ArC) 129.2 (ArC) 129.7 (ArC) 130.9 (PMP-C) 132.0 (PMP-C) 136.5 (q, ArC) 138.8 (q, ArC) 157.5 (q, *J* = 34.6, COCF<sub>3</sub>) 160.0 (q, ArCO) further signals indistinguishable; <sup>19</sup>F NMR (CDCl<sub>3</sub>, 282 MHz)  $\delta$  – 67.5 ppm (3F, s, CF<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 927 (54 %, 2M + H + Na<sup>+</sup>) 475 (96 %, M + Na<sup>+</sup>) 470 (74 %, M + NH<sub>4</sub><sup>+</sup>) 453 (97 %, M + H<sup>+</sup>) 234 (C<sub>17</sub>H<sub>16</sub>N); HRMS (C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>) calcd. 453.1784, found 453.1782.

### 3.3.14 Miscellaneous substances

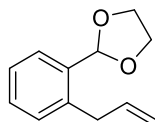
#### Potassium vinyltrifluoroborate (**417**)



To a solution of B(OMe)<sub>3</sub> (2.6 mL, 22.8 mmol) in dry THF (15 mL) under N<sub>2</sub> at -78 °C was added vinyl magnesium bromide (0.90 M in THF, 20.0 mL, 18.0 mmol) and stirred at -78 °C for 20 min before allowing to warm to rt over 1h. The mixture was cooled to 0 °C and KHF<sub>2</sub> (6.98 g, 89.2 mmol) was added followed by the addition of water (12 mL) over 30 min. The reaction was stirred at rt for 1 h before the reaction was stopped and conc *in vacuo*. The crude material was dissolved in acetone, filtered and conc *in vacuo*. Purification by recrystallisation (Me<sub>2</sub>CO/Et<sub>2</sub>O) afforded **417** (1.72 g, 13.0 mmol, 71 %) mp 227.3 – 231 °C (lit<sup>219</sup> 225 °C (dec)); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.82 – 5.93 (1H, m) 5.28 (1H, br m) 5.16 (1H, br m).

**Allyl diethylmalonate (414)**

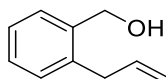
A mixture of diethyl malonate (58.0 mL, 0.38 mol, 1.5 eq), allyl bromide (21.5 mL, 0.25 mol, 1 eq) and  $K_2CO_3$  (104 g, 0.75 mol, 3 eq) in acetone (1.3 L) was stirred at rt for 2 d. The reaction was quenched by sat aq.  $NH_4Cl$  (1 L) and the acetone was removed *in vacuo*. The aqueous layer was extracted with  $CH_2Cl_2$  (600 mL x 3), the combined organic layers were washed with brine (400 mL) dried ( $MgSO_4$ ), filtered and concentrated *in vacuo*. Purification by distillation (104 – 106 °C, 23 - 26 mmHg) and flash column chromatography (0 – 5 % EtOAc/Hexanes) afforded **414** as a colourless oil (27.5 g, 137 mmol, 55 %);  $^1H$  NMR ( $CDCl_3$ , 600 MHz)  $\delta$  1.23 (6H, t,  $J = 7.2$ ,  $CH_3$ ) 2.61 (2H, apt t,  $J = 7.2$ ,  $CHCH_2CHCH_2$ ) 3.39 (1H, t,  $J = 7.5$ ,  $COCHCO$ ) 4.18 (4H, m,  $CH_2CH_3$ ) 5.03 (1H, dd,  $J = 10.2$ , 1.2,  $CHCH_2$ -*cis*) 5.10 (1H, dd,  $J = 17.1$ , 1.5,  $CHCH_2$ -*trans*) 5.75 (1H, ddt,  $J = 17.0$ , 10.2, 6.9,  $CH_2CHCH_2$ );  $^{13}C$  NMR ( $CDCl_3$ , 125 MHz) 14.2 (2C,  $CH_3$ ) 32.9 ( $CHCH_2CH$ ) 51.7 ( $CHCH_2CHCH_2$ ) 61.5 (2C,  $CH_2O$ ) 117.6 ( $CH_2CHCH_2CH$ ) 134.2 ( $CH_2CHCH_2CH$ ) 169.0 (2C, q, CO). NMR data consistent with published data.<sup>296</sup>

**2-(2-allylphenyl)-1,3-dioxolane (504)**

To a solution of aryl bromide **462** (0.75 mL, 5.03 mmol) in dry  $Et_2O$  (15 mL) under  $N_2$  at -78 °C was added dropwise  $nBuLi$  in Hexanes (1.37 M, 4.0 mL, 5.48 mmol) giving an orange colour. The reaction was stirred for 2 h at -78 °C before dropwise addition of allyl bromide (1.15 mL, 13.3 mmol) and the solution was allowed to warm to rt o/n. On completion of the reaction by TLC analysis, the reaction mixture was quenched with sat.  $NH_4Cl$  solution (20 mL) and extracted with  $Et_2O$  (20 mL x 3). The combined organic extracts were washed with brine (50 mL), dried ( $MgSO_4$ ) filtered and concentrated *in vacuo*. Purification by flash column chromatography (2-6 % EtOAc/Petroleum ether) afforded **504** as a colourless oil (0.76 g, 4.00 mmol, 80 %);  $^1H$  NMR ( $CDCl_3$ , 600 MHz)  $\delta$  3.57 (2H, dt,  $J = 6.4$ , 1.5,  $ArCH_2$ ) 4.10 (4H, m,  $OCH_2CH_2O$ ) 5.04 (1H, dq,  $J = 17.1$ , 1.8,  $ArCH_2CHCH_2$ -*trans*) 5.09 (1H, dq,  $J = 10.3$ , 1.5,  $ArCH_2CHCH_2$ -*cis*) 6.01 (1H, s,

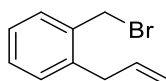
ArCHO<sub>2</sub>) 6.02 (1H, ddd,  $J = 17.0, 10.2, 6.3$ , ArCH<sub>2</sub>CHCH<sub>2</sub>) 7.19 -7.36 (3H, m, ArH) 7.60 (1H, dd,  $J = 7.5, 1.8$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.6 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 65.4 (O<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>) 101.7 (CHO<sub>2</sub>) 116.0 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 126.2 (ArC) 126.5 (ArC) 129.3 (ArC) 130.0 (ArC) 135.4 (q, ArCCHO<sub>2</sub>) 137.3 (ArCCH<sub>2</sub>CHCH<sub>2</sub>) 138.5 (ArCCH<sub>2</sub>CHCH<sub>2</sub>). NMR data consistent with published data.<sup>259</sup>

**(2-allylphenyl)methanol (505)**



To a solution of LiAlH<sub>4</sub> (0.78 g, 20.5 mmol) in dry Et<sub>2</sub>O (60 mL) under N<sub>2</sub> at rt was added aldehyde **358u** (6.00 g, 41.0 mmol) in dry Et<sub>2</sub>O (110 mL) and the reaction was stirred at rt for 30 min until complete by TLC analysis. Breaking up of LiAlH<sub>4</sub> was achieved by the careful addition of H<sub>2</sub>O before pouring into ice-water (500 mL). The aqueous layer was extracted with Et<sub>2</sub>O (500 mL x 3), dried (K<sub>2</sub>CO<sub>3</sub>), filtered and concentrated *in vacuo*, affording alcohol **505** as a light orange oil used without further purification (5.44 g, 36.7 mmol, 90 %); R<sub>F</sub> = 0.31 (15 % EtOAc/Petroleum ether); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) 2.42 (1H, br s, OH) 3.47 (2H, d,  $J = 6.3$ , ArCH<sub>2</sub>CH) 4.66 (2H, s, ArCH<sub>2</sub>OH) 5.03 (1H, d,  $J = 17.0$ , ArCH<sub>2</sub>CHCH<sub>2-trans</sub>) 5.10 (1H, d,  $J = 10.2$ , ArCH<sub>2</sub>CHCH<sub>2-cis</sub>) 6.01 (1H, ddt,  $J = 17.0, 10.2, 6.3$ , ArCH<sub>2</sub>CHCH<sub>2</sub>) 7.22 (1H, d,  $J = 7.2$ , ArH) 7.24 – 7.30 (2H, m, ArH) 7.39 (1H, d, ArH); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz)  $\delta$  36.9 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 63.3 (ArCH<sub>2</sub>OH) 116.0 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 126.8 (ArC) 128.2 (ArC) 128.4 (ArC) 130.0 (ArC) 137.6 (ArCH<sub>2</sub>CHCH<sub>2</sub>) 137.9 (q, ArCCH<sub>2</sub>CHCH<sub>2</sub>) 138.7 (ArCCH<sub>2</sub>OH). NMR data consistent with published data.<sup>243</sup>

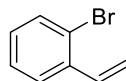
**1-allyl-2-(bromomethyl)benzene (506)**



To a solution of alcohol **505** (5.44 g, 36.7 mmol) in DCE (60 mL) under N<sub>2</sub> at 0 °C was added dropwise PBr<sub>3</sub> (10.5 mL, 48.6 mmol) over 15 min and the reaction was stirred in an ice bath for 45 min before allowing to warm to rt for 15 min until complete by TLC analysis. The reaction was quenched by addition of ice-water (150 mL) at 0 °C, and the layers were separated. The aqueous layer was extracted with EtOAc (200 mL x 3), washed with brine (500 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Purification by

flash column chromatography (10 % EtOAc/hexanes) to give product **506** as a pale yellow oil (7.35 g, 34.8 mmol, 95 %);  $R_F$  = 0.78 (20 % EtOAc/Petroleum ether);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  3.55 (2H, dt,  $J$  = 6.2, 1.5,  $\text{ArCH}_2\text{CHCH}_2$ ) 4.55 ( $\text{ArCH}_2\text{Br}$ ) 5.05 (1H, apt dq,  $J$  = 17.1, 1.7,  $\text{ArCH}_2\text{CHCH}_2\text{-trans}$ ) 5.11 (1H, apt dq,  $J$  = 10.1, 1.6,  $\text{ArCH}_2\text{CHCH}_2\text{-cis}$ ) 6.02 (1H, ddt,  $J$  = 17.1, 10.1, 6.3) 7.20 – 7.29 (3H, m,  $\text{ArH}$ ) 7.35 (1H, d,  $J$  = 7.5,  $\text{ArH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 150 MHz)  $\delta$  31.8 ( $\text{CH}_2\text{Br}$ ) 36.8 ( $\text{ArCH}_2\text{CHCH}_2$ ) 116.4 ( $\text{ArCH}_2\text{CHCH}_2$ ) 127.1 ( $\text{ArC}$ ) 129.3 ( $\text{ArC}$ ) 130.4 ( $\text{ArC}$ ) 130.7 ( $\text{ArC}$ ) 135.9 (q,  $\text{ArCCH}_2\text{Br}$ ) 136.6 ( $\text{ArCH}_2\text{CHCH}_2$ ) 138.9 ( $\text{ArCCH}_2\text{CHCH}_2$ ). NMR data consistent with published data.<sup>243</sup>

### 1-bromo-2-vinylbenzene (**419**)



To a solution of methyltriphenylphosphonium bromide (93.0 g, 0.26 mol) in  $\text{CH}_2\text{Cl}_2$  (1 L) under  $\text{N}_2$  at reflux was added DBU (42.0 mL, 0.28 mol) and the reaction stirred at reflux for 80 min. To this solution at reflux was added a solution of 2-bromobenzaldehyde (15.0 mL, 0.13 mol) in  $\text{CH}_2\text{Cl}_2$  (400 mL) and the reaction was stirred for 2 d until complete. The reaction was cooled and washed with  $\text{H}_2\text{O}$  (400 mL x 5) dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. Purification via short silica plug vacuum chromatography (25 % PhMe/Hexanes) afforded **419** as a colourless oil (16.1 g, 88.0 mmol, 69 %);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  5.38 (1H, dd,  $J$  = 11.0, 0.9,  $\text{CH}_2\text{-cis}$ ) 5.72 (1H, dd,  $J$  = 17.4, 1.1,  $\text{CH}_2\text{-trans}$ ) 7.08 (1H, dd,  $J$  = 17.4, 10.9,  $\text{CHCH}_2$ ) 7.12 (1H, m,  $\text{ArH}$ ) 7.29 (1H, tm,  $\text{ArH}$ ) 7.57 (2H, apt dd,  $J$  = 8.0, 1.4,  $\text{ArH}$ ). NMR data consistent with published data.<sup>297</sup>

## Chapter 4: Appendices

### 4.1 Abbreviations

ABCN	1,1'-Azobis(cyclohexanecarbonitrile)
Ac	Acetyl
AIBN	2,2'-Azobis(2-methylpropionitrile)
alloc	allyloxycarbonyl
apt	Apparent
aq.	Aqueous

Ar	Aromatic
atm	Atmospheres
Aux	Auxiliary
B	Base
BINOL	1,1'-Bi(2-naphthol)
Bn	Benzyl
BNAH	1-benzyl-1,4-dihydronicotinamide
Boc	tert-Butoxycarbonyl
BOX	Bisoxazoline
br	broad
Bu	Butyl
Bz	Benzoyl
C <sub>6</sub> H <sub>6</sub>	Benzene
Calcd.	Calculated
CAN	Ceric(IV) ammonium nitrate
Cbz	Carboxybenzyl
Conc.	Concentrated
COSY	Correlation spectroscopy
Cy	Cyclohexyl
δ	Chemical shift
d	days (or doublet, <sup>1</sup> H NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEAD	diethylazodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
<i>dig</i>	Digonal
DIPEA	Diisopropylethylamine

DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
eq. or equiv.	Equivalents
Et	Ethyl
EWG	Electron withdrawing group
Fmoc	Fluorenylmethoxycarbonyl
h	Hours
HetAr	Heterocycle
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
<sup>i</sup> Bu	Isobutyl
<sup>i</sup> Pr	Isopropyl
IR	Infrared
<i>J</i>	Coupling constant
LDA	Lithium diisopropylamide
LG	Leaving group
Lit.	Literature
LUMO	Lowest unoccupied molecular orbital
<i>m</i> CPBA	<i>meta</i> -chloroperoxybenzoic acid

Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
mmol	Millimole(s)
MOM	Methoxymethyl ether
mp	Melting point
Ms	methanesulfonyl
MS	Molecular sieves (also Mass spectroscopy)
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMR	Nuclear magnetic resonance
Ns	p-nitrobenzenesulfonyl
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
o/n	Overnight
Oct	Octanyl
OMB	ortho-Methoxybenzyl
OMP	ortho-Methoxyphenyl
Pent	Pentyl
PG	Protecting group
Ph	Phenyl
PhMe	Toluene
PMB	para-Methoxybenzyl
PMP	para-Methoxyphenyl

ppm	Parts per million
Pr	Propyl
pTSA	para-Toluenesulfonic acid
Py	Pyridine
q	Quaternary
RSM	Recovered starting material
rt	Room temperature
sat.	Saturated
SET	Singlet electron transfer
SM	Starting material
S <sub>N</sub> 2	Bimolecular nucleophilic substitution
S <sub>RN</sub> 1	Unimolecular radical nucleophilic substitution
SOMO	Singly occupied molecular orbital
TBAF	tetra <i>n</i> -butylammonium fluoride
TBDMS/TBS	tert-Butyldimethylsilyl
<sup>t</sup> Bu	tert-Butyl
TBTH	tri- <i>n</i> -butyltin hydride
Tf	Triflate
TFA	Trifluoroacetic acid/Trifluoroacetyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin Layer Chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	para-Tolyl
TPTH	tri-phenyltin hydride
<i>trig</i>	Trigonal
Ts	p-toluenesulfonyl
TS	Transition state



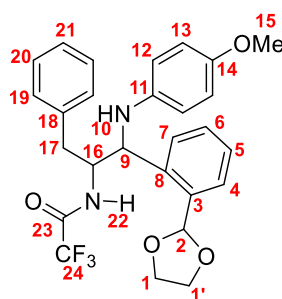
Å	Angstrom
°C	Degrees Centigrade
)))	Sonication

NOE correlation abbreviations:

s	strong
m	medium
w	weak
n	no correlation

## 4.2 Data correlation tables

### 4.2.1 1,2-aminoacetamides

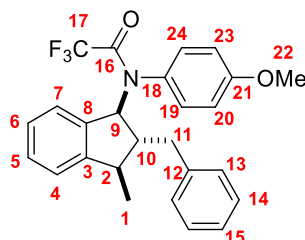


**101am**

$\delta_H$ / ppm	Mult.	#	COSY	$\delta_C$ / ppm	HMBCs
3.15	1H, dd	17	16, 17'	36.8	9, 16, 18, 19
3.31	1H, m	1	1, 1'	64.5	1', 2
3.37	1H, dd	17'	16, 17	36.8	16, 18, 19
3.69	3H, s	15	-	55.7	14
3.72 -3.79	3H, m	1, 1'	1	64.8	1, 1', 2
4.07	1H, br s	10	-	-	-
4.28	1H, m	16	9, 17, 17', 22	55.8	9, 17, 18, 23
4.87	1H, d	9	16	53.0	(3 or 8), 7, 11, 16, 17,
5.61	1H, s	2		104.8	1, (3 or 8), 11
6.65	2H, dm	13	-	115.2	12
6.70	2H, dm	12	-	114.9	11, 13
7.20	3H, m	19 & Ar		127.7, 130.7 (2C)	
7.27 – 7.36	5H, m	Ar peaks		127.0, 128.6 (3C), 130.9	
7.47	1H, d	7		126.0	9
8.20	1H, d	22	16	-	23
-		24		115.8	-
-		(3 or 8)		132.9	2, 7, 9

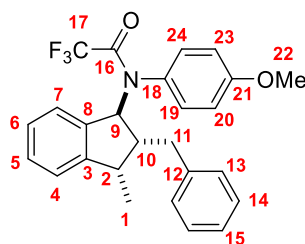
-	<b>18</b>	136.4	16, 17
-	<b>11</b>	140.2	12, 13
-	<b>(3 or 8)</b>	140.4	2, 9
-	<b>14</b>	152.6	12, 13
-	<b>23</b>	156.5	22

## 4.2.2 Indanes



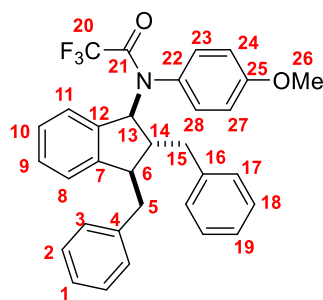
437a

$\delta_{\text{H}} / \text{ppm}$	Mult.	$J_{\text{HH}} / \text{Hz}$	#	COSY	$\delta_{\text{C}} / \text{ppm}$	HMBCs	NOEs
<b>0.97</b>	3H, d	7.0	<b>1</b>	2, 10(w)	18.8	2, 9(w), 10	
<b>1.99</b>	tdd	8.7, 7.6, 6.1	<b>10</b>	1(w), 2, 9, 11'	51.4	1, 2, 11, 11', 9	<b>2</b> (-) <b>11</b> (m)
<b>2.85</b>	m	-	<b>2</b>	1, 10	42.6	1, 10, 11, 11', & ArH	
<b>2.95</b>	dd	13.7, 6.0	<b>11</b>	10, 11'	39.2	2, 9, 10, ArH	
<b>3.03</b>	dd	13.7, 7.5	<b>11'</b>	10, 11	39.2	2, 9, 10, ArH	
<b>3.76</b>	3H, s		<b>22</b>		55.4	-	
<b>6.28</b>	d	8.8	<b>9</b>	2, 10	67.0	10, 11, 11'	<b>2</b> (w) <b>10</b> (m) <b>11</b> (m)
<b>6.37</b>	Apt d	8.6	<b>PMP</b>		113.6	-	
<b>6.59</b>	dd	8.9, 2.9	<b>PMP</b>		132.1		
<b>6.61-6.65</b>	m	-	<b>PMP</b>				
<b>6.76</b>	dd	8.8, 2.9	<b>PMP</b>				
<b>7.09-7.13</b>	2H, m	-	<b>ArH</b>				
<b>7.23-7.39</b>	7H, m	-	<b>ArH</b>				
		$^1J_{\text{CF}} = 288.3$	<b>17</b>		116.6	-	
			<b>18</b>		127.9	9, PMP	
			<b>8</b>		139.6	2, 9, 10	
			<b>12</b>		139.6	10, 11, 11'	
			<b>3</b>		146.7	1, 2, 9, ArH	
		$^2J_{\text{CF}} = 35.1$	<b>16</b>		158.2		
			<b>21</b>		159.8		

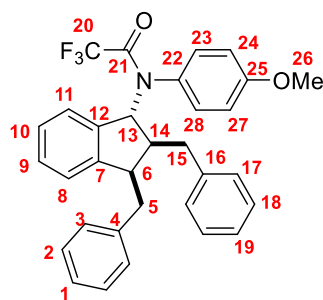
**437b**

$\delta_H / ppm$	Mult.	$J_{HH} / Hz$	#	COSY	$\delta_C / ppm$	HMBCs	NOEs
<b>1.12</b>	3H, d	7.3	<b>1</b>	(2/11') <sup>a</sup> (w)	9 17.3	(2/11') <sup>a</sup> , 10	
<b>2.60</b>	tdd	9.2, 7.9, 6.7	<b>10</b>	(2/11') <sup>a</sup> , 9	39.3	1, 11	<b>2</b> (s) <b>9</b> (w) <b>11</b> (-)
<b>2.90</b>	dd	14.5, 9.2	<b>11</b>	10	34.4	1, (2/11') <sup>a</sup> , 9, 10	
<b>2.96- 3.04</b>	2H, m		<b>11'</b> & <b>2</b>	1, 10	34.4 & 45.3	1, (2/11') <sup>a</sup> , 9, 11	
<b>3.77</b>	3H, s		<b>22</b>	-	55.5		
<b>6.24</b>	d	9.2	<b>9</b>	10, ArH	66.3	(2/11') <sup>a</sup> , 10, 11, ArH	<b>10</b> (w) <b>2</b> (-) <b>11</b> (m)
<b>6.61- 6.65</b>	m		<b>PMP</b>		113.6 - 132.1		
<b>6.70</b>	dm	8.7	<b>PMP</b>				
<b>6.83</b>	m		<b>PMP</b>				
<b>7.18</b>	2H, apt d	7.5	<b>ArH</b>				
<b>7.23- 7.39</b>	7H, m		<b>ArH</b>				
		<sup>1</sup> J <sub>CF</sub> = 289.2	<b>17</b>		116.6		
			<b>18</b>		127.8	9, PMP	
			<b>8</b>		139.1	9, ArH	
			<b>12</b>		140.0	10, 11, 11', ArH	
			<b>3</b>		148.7	1, 2/11', 9, ArH	
		<sup>2</sup> J <sub>CF</sub> =34.6	<b>16</b>		158.5	9	
			<b>21</b>		160.0	PMP	

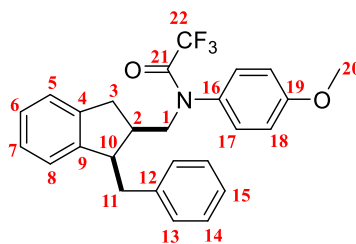
<sup>a</sup>Coincident signals

**477a**

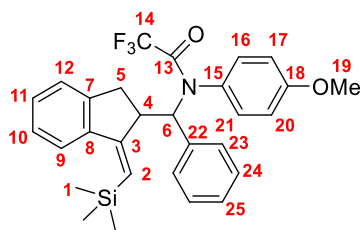
$\delta_H$ / ppm	Mult.	$J_{HH}$ / Hz	#	$\delta_C$ / ppm	HMBCs	NOEs
2.21	1H, dtd	9.6, 7.1, 4.8,	14	47.5		13 (w)
2.24	1H, dd	13.4, 8.2	5	41.2		
2.51	1H, dd	13.3, 4.6	15	41.0		
2.70	1H, dd	13.4, 9.6	15'	41.0		
2.79	1H, dd	13.6, 6.3	5'	41.2		
3.13 – 3.18	m		6	49.8		13 (m) 14 (w)
3.78	3H, s	-	26	55.5		
6.17	1h, d	7.8	PMP			
6.31	1H, d	7.1	13	67.3		
6.42	1H, dd	8.7, 2.6	PMP			
6.54	1H, dd	8.9, 3.0	PMP			
6.75	1H, dd	8.8, 3.0	PMP			
6.91	2H, m	-	Ar			
7.05	3H, apt d	7.0	Ar		12	
7.15 – 7.35	8H, m	-	Ar		12, 7	
7.37	1H, d	7.4	Ar		7	
		288.7	20	116.6		
			22	128.0	PMP	
			4	139.3	5	
			16	139.6	15	
			12	140.2	13	
			7	145.6	5, 6, 13	
		34.8	21	157.6		
			25	159.8		

**477b**

$\delta_H / ppm$	Mult.	$J_{HH} / Hz$	#	COSY	$\delta_C / ppm$	HMBCs	NOEs
2.44	1H, dd	13.4, 8.2	5		36.5	6, 14	13 (m)
2.69	1H, m		14	6, 13, 15	46.0	5', 6, 13, 15	6 (s)
3.05	2H, m		15	14	34.1	13, 14	13 (s)
3.10	1H, ddd	10.8, 7.5, 5.0	6	5, 14	46.2	5, 14	
3.13	– 1H, m		5'		36.5	6, 14	
3.18							
3.78	3H, s		26		55.5		
6.24	1H, d	7.3	Ar				
6.28	1H, d	9.2	13	14	66.0	6, 14, 15	5 (m) 5' (s)
6.63	1H, dd	8.9, 2.9	PMP				
6.69	1H, dd	8.9, 2.5	PMP				
6.78	2H, m		Ar				
6.86	1H, dd	8.8, 2.9	PMP				
6.95	1H, m		PMP				
7.00	1H, apt t	7.4	Ar				
7.15	– 9H, m		Ar				
7.35							
7.40	1H, d	7.6	Ar				
		289.4	20		116.7		
			22		127.8		
			16		139.5		
			12		139.6		
			4		139.8		
			7		145.7		
		34.7	21		158.6		
			25		160.1		

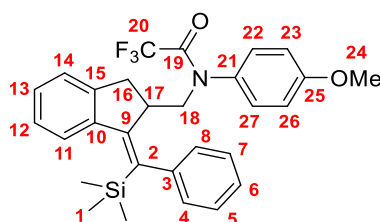
**421**

$\delta_{\text{H}} / \text{ppm}$	Multipl.	$J_{\text{HH}} / \text{Hz}$	#	COSY	$\delta_{\text{C}} / \text{ppm}$	HMBCs	NOEs
2.61	dd	13.3, 10.3	11'	10, 11	35.4	-	
2.72	m	-	2	1, 1', 3	41.5	1,1',10,3,11,11'	10 (s)
2.90	dd	13.4, 6.0	11	10, 11'	35.4	13,2,10	
2.93	2H, d	8.2	3	2	35.2	5,1,1',(10	
3.36	dt	10.2, 6.5	10	2, 11, 11'	48.0	8,1,1',3,11,11',2	2 (s)
3.74	dd	13.3, 5.3	1'	1, 2	52.0	-	
3.84	s		20		55.6	-	
4.31	dd	13.3, 9.8	1	1', 2	52.0	3,2	
6.42	d	7.5	8		125.0	6	
6.87 – 6.92	m		18		~115.0 br		
6.94	td	7.5, 1.0	7		125.8	5	
6.96 – 7.00	m		13		129.4	3,3'	
7.13	td	7.5, 0.9	6		126.9	8	
7.15	m		17		~130 br		
-	m		15		126.2	13o	
7.25	d	7.5	5		124.7	3	
-	m		14		128.3		
-		$^1J_{\text{CF}} = 288.6$	22		116.6		
-			16		131.2	17,18,1,1'	
-			12		139.8	14,10,11,11'	
-			4		141.8	6,8,10,3	
-			9		145.6	5, 7, 10,3,11,11'	
-		$^2J_{\text{CF}} = 34.9$	21		157.5	1, 1'	
-			19		159.9	17, 18, 20	



517

$\delta_{\text{H}}$ / ppm	Mult.	$J_{\text{HH}}$ / Hz	#	COSY	$\delta_{\text{C}}$ / ppm	HMBCs	NOEs
0.29	9H, s		1		0.05		9
2.27	1H, apt d	16.7	5	4	35.5	3, 4, 6, 7, 8, 12	
3.04	1H, dd	16.6, 7.5	5'	4, 12	35.5	4, 6, 7, 8	
3.78	3H, s		19		55.5	18	
4.21	1H, br dd	10.8, 7.5	4	5', 6	48.0	5, 5', 6, 7	2
4.55	1H, br d	10.8	6	4	71.1 (br)	4, 5, 5'	
5.99	1H, s		2	4	124.8	1, 2, 4, 6, 8	4, PMP
6.67	1H, dd	8.9, 3.0	PMP		114.3		
6.71 – 6.74	1H, m		PMP		131.2		2
6.80	1H, dd	8.7, 2.7	PMP		113.5		
7.07	1H, m		PMP		130.1		2
7.11	1H, d	7.5	12	5'	125.7	5, 8	
7.18 - 7.31	7H, m		ArH				
7.67	1H, d	7.7	9		124.6	2, 7	1
			15		130.4		
			22		137.3		
			8		140.4	2, 5, 5', 12	
			7		145.7	4, 5, 5', 9	
		35.5	14		156.9		
			3		159.3	2, 5, 9	
			18		159.6	19	

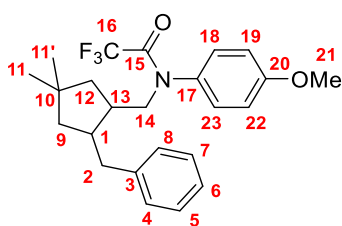


518

$\delta_{\text{H}}$ / ppm	Mult.	$J_{\text{HH}}$ / Hz	#	$\delta_{\text{C}}$ / ppm	HMBCs
0.07	9H, s		1	0.5	1
2.72	1H, apt d	15.4	16	33.5	13, 14, 15, 17, 18
2.90	1H, dd	13.3, 3.3	18	52.3	16, 17
2.93 – 3.03	2H, m		16 & 17	33.5 & 42.1	16 (12, 13, 15, 17, 18) 17 (qs)
3.85	3H, s		24	55.6	(qs)
4.01	1H, dd	13.1, 11.5	18	52.3	16, 17,

<b>6.60 – 7.17</b>	9H, br m			
<b>7.24</b>	1H, apt t	<b>12</b>	126.0	
<b>7.28</b>	1H, dd	<b>13</b>	128.8	
<b>7.32</b>	1, d	<b>14</b>	126.3	15
<b>7.66</b>	1H, d	<b>11</b>	125.5	15
		<b>21</b>	130.0	18
		<b>2</b>	139.4	1, 17
		<b>15</b>	139.8	11, 14, 16,
		<b>3</b>	145.2	(Ar)
		<b>10</b>	146.6	11, 16, 17,
		<b>9</b>	153.5	11, 16, 17, 18
		<b>19</b>	157.6	18
		<b>25</b>	159.3	24

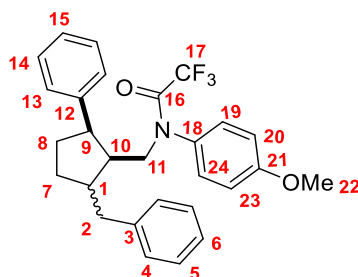
### 4.2.3 Cyclopentanes



491

$\delta_H$ / ppm	Mult.	$J_{HH}$ / Hz	#	COSY	$\delta_C$ / ppm
<b>0.92</b>	3H, s	-	<b>11</b>		30.6
<b>1.11</b>	3H, s	-	<b>11'</b>		31.4
<b>1.34</b>	1H, dd	13.0, 8.5	<b>9</b>		46.3
<b>1.40</b>	1H, dd	13.0, 6.6	<b>9</b>		46.3
<b>1.50</b>	1H, dd	13.0, 7.8	<b>12</b>		44.7
<b>1.58</b>	1H, dd	13.0, 7.3	<b>12</b>		44.7
<b>2.27</b>	1H, m		<b>13</b>	12, 14	38.8
<b>2.38</b>	1H, m		<b>1</b>	9, 13	42.4
<b>2.43</b>	1H, dd	12.8, 10.7	<b>2</b>	4/8	36.5
<b>2.70</b>	1H, dd	12.8, 4.7	<b>2</b>	4/8	36.5
<b>3.49</b>	1H, dd	13.1, 4.9	<b>14</b>	13	52.4
<b>3.85</b>	3H, s	-	<b>21</b>		55.6
<b>4.25</b>	1H, dd	13.0, 11.0	<b>14</b>		52.4
<b>6.91</b>	2H, apt d	8.7	<b>19 &amp; 22</b>		114.0, 114.7
<b>7.08</b>	2H, apt d	7.8	<b>4 &amp; 8</b>		128.8
<b>7.11</b>	2H, d	8.6	<b>18 &amp; 23</b>		129.4, 130.0
<b>7.16</b>	1H, tm	7.4	<b>6</b>		125.9
<b>7.22 – 7.25</b>	2H, m	-	<b>5 &amp; 7</b>		128.4
			<b>10</b>		37.4

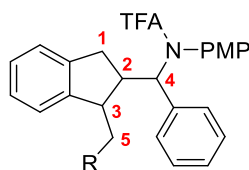


**493**

$\delta_H$ / ppm	Mult.	$J_{HH}$ / Hz	#	COSY	$\delta_C$ / ppm	HMBCs	NOESY
1.54	m	-	7	7', 1/2	30.9		
1.61	1H, m	-	8	8'	34.8		
1.74	1H, m	-	7'	7, 8', 1	30.9		
2.25 –	2H, m	-	8' &	(7, 8', 7')	34.8		
2.33			10	(11, 8, 9)	47.6		1 (w) 9 (s)
2.40 –	2H, m	-	2 &	7	35.7,		
2.47			1		44.1		9 (w) 10 (w)
2.77	1H, m	-	2'	1/2	35.7		
3.13	1H, apt q	8.4	9	10	49.1		10 (s) 1 (w)
3.62	1H, dd	13.5, 6.0	11	10	52.7		
3.79	3H, s	-	22				
4.28	1H, dd	13.4, 9.1	11	10	52.7		
			18		131.0 (q)	11	
			3		141.2 (q)	2	
			12		146.6 (q)	9	
			16		157.6 (q)	11	
			21		159.5 (q)	22	

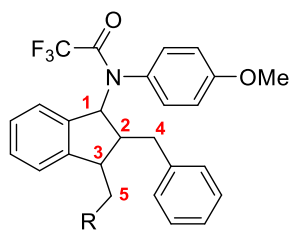
### 4.3 *J* coupling tables

#### 4.3.1 Indanes



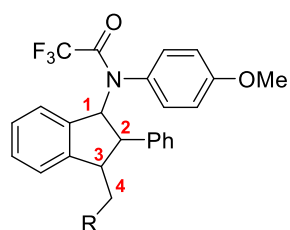
Protons	470a NOE	$J$ /Hz	470b NOE	$J$ /Hz	471a NOE	$J$ /Hz	471b NOE <sup>a</sup>	$J$ /Hz
1 - 2	s	9.5	a	12.6	-	-	-	7.2
1' - 2	s	9.5	a	-	-	-	-	-
2 - 4	n	12.1	n	6.9	w	-	-	-
2 - 3	s	6.8	s	6.7	a	6.6	-	7.2
3 - 5	w	10.9	s	11.5	-	11.2	-	7.2
3 - 5'	s	4.0	n	3.9	-	3.4	-	7.3

NOEs = s – strong, m – medium, w – weak, n – no correlation <sup>a</sup>not run



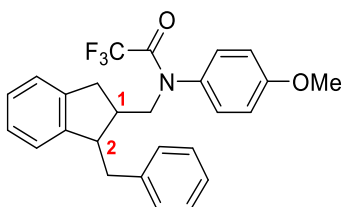
Protons	<b>437a</b>		<b>437b</b>		<b>477a</b>		<b>477b</b>		<b>478</b>	
	NOE	<i>J</i> /Hz	NOE	<i>J</i> /Hz	NOE	<i>J</i> /Hz	NOE	<i>J</i> /Hz	NOE	<i>J</i> /Hz
1 – 2	m	8.8	w	9.2	w	7.1	w	9.2	w	7.6
2 – 3	n	8.7	s	6.7	w	~ 7	s	7.5	w	~7.1
1 – 3	w	-	n	-	w	-	n	-	n	-
1 – 4	-	-	-	-	s	-	-	-	-	-
2 – 4	-	6.1	-	9.2	-	9.6	-	-	-	-
2 – 4'	-	7.6	-	7.9	-	4.8	-	-	-	-
1 – 5	-	-	-	-	-	-	m	-	-	-
1 – 5'	-	-	-	-	-	-	s	-	-	-
3 – 5	-	-	-	-	-	8.2	w	8.5	-	-
3 – 5'	-	-	-	-	-	6.3	-	-	-	-

NOEs = s – strong, m – medium, w – weak, n – no correlation



Protons	<b>509</b>	
	NOE	<i>J</i> /Hz
1 – 2	w	9.4
2 – 3	w	~ 9.0
1 – 3	m	-
3 – 4	-	5.0
3 – 4'	-	7.9

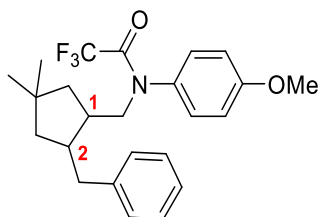
NOEs = s – strong, m – medium, w – weak, n – no correlation



Protons	<b>421</b>	
	NOE	<i>J</i> /Hz
1 – 2	s	~ 6.9

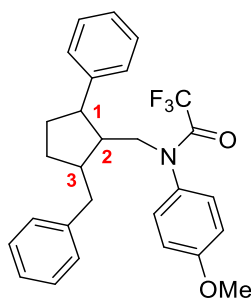
NOEs = s – strong, m – medium, w – weak, n – no correlation

### 4.3.2 Cyclopentanes



Protons	<b>491</b>	
	NOE	<i>J</i> /Hz
1 – 2	m – s	-

NOEs = s – strong, m – medium, w – weak, n – no correlation



Protons	<b>493</b>	
	NOE	<i>J</i> /Hz
1 – 2	s	8.2
2 – 3	w	-
1 – 3	w	-

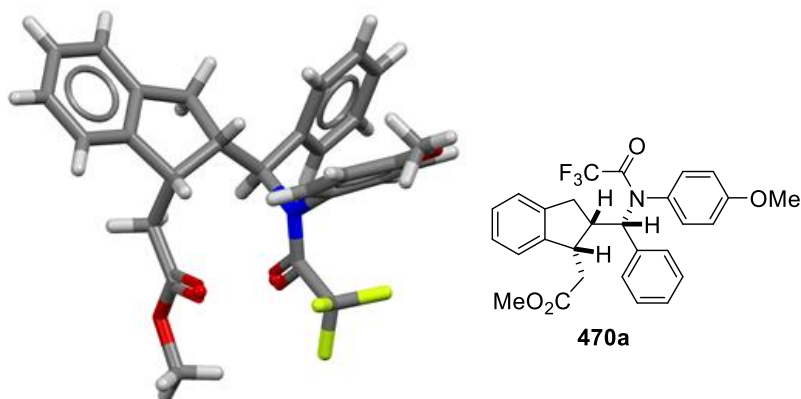
## 4.4 X-Ray crystallography data

### 4.4.1 General information

The single crystal X-ray diffractometer is equipped with an Atlas CCD Detector. All data sets collected at 150 K using CuK $\alpha$  radiation ( $\lambda = 1.54184$  Å). The data were acquired and processed using the CrysAlis<sup>Pro</sup> program.<sup>298</sup> The datasets were corrected for Lorentz and polarization effects. Structure solution and refinement were accomplished using SHELXS-97 and SHELXL-97,<sup>299</sup> respectively. The crystal structures were solved using direct methods. All non-hydrogen atoms were refined anisotropically, while hydrogen atoms associated with carbon and oxygen atoms were refined isotropically in geometrically constrained positions. Hydrogen atoms affiliated with nitrogen atoms were refined isotropically in positions identified in the difference Fourier map. Crystallographic and refinement parameters for crystal structures in section 4.4.2.

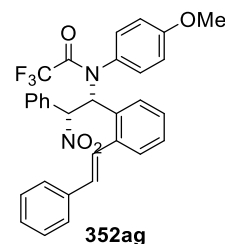
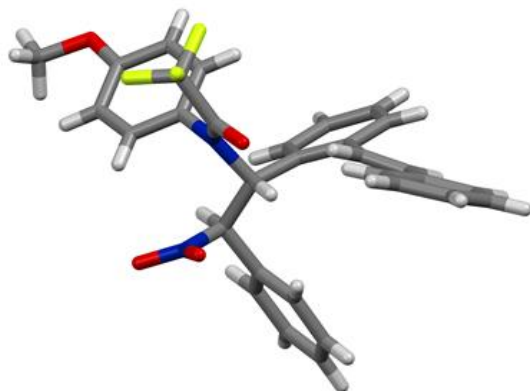
## 4.4.2 Crystal structures

**methyl 2-((1*R*\*,2*R*\*)-2-((*R*\*)-phenyl(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)methyl)-2,3-dihydro-1*H*-inden-1-yl)acetate (470a)**



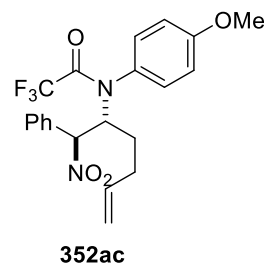
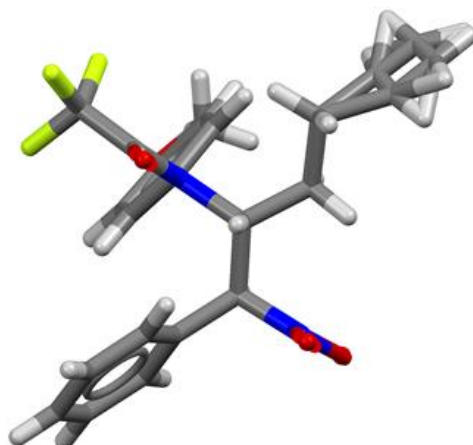
chemical formula	C <sub>28</sub> H <sub>26</sub> F <sub>3</sub> NO <sub>4</sub>	
<i>M<sub>r</sub></i> /g mol <sup>-1</sup>	497.50	
crystal system	monoclinic	
space group	<i>P</i> 2 <sub>1</sub> / <i>c</i>	
Unit cell dimensions	<i>a</i> = 15.1930(3) Å	<i>α</i> = 90°
	<i>b</i> = 13.0292(2) Å	<i>β</i> = 110.560(3)°
	<i>c</i> = 12.8223(3) Å	<i>γ</i> = 90°
Volume	2376.54(9) Å <sup>3</sup>	
<i>Z</i>	4	
Density (calculated)	1.39 cm <sup>-3</sup>	
<i>F</i> (000)	1040	
<i>μ</i> (CuKα)	0.912 mm <sup>-1</sup>	
<i>T</i> /K	150(2)	
	−18 → 18	
index range	−15 → 15	
	−15 → 10	
collected reflections	34570	
unique reflections	4198	
<i>R</i> <sub>int</sub>	0.1108	
reflections with <i>I</i> > 2σ( <i>I</i> )	3452	
no. parameters	325	
<i>R</i> ( <i>F</i> ), <i>F</i> > 2σ( <i>F</i> )	0.0426	
<i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>F</i> > 2σ( <i>F</i> )	0.11	
<i>R</i> ( <i>F</i> ), all data	0.0529	
<i>wR</i> ( <i>F</i> <sup>2</sup> ), all data	0.1171	
Δ <sub>r</sub> (min., max.) e Å <sup>-3</sup>	−0.225, 0.238	

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*\*,2*R*\*)-2-nitro-2-phenyl-1-(2-((*E*)-styryl)phenyl)ethyl)acetamide (352ag)**



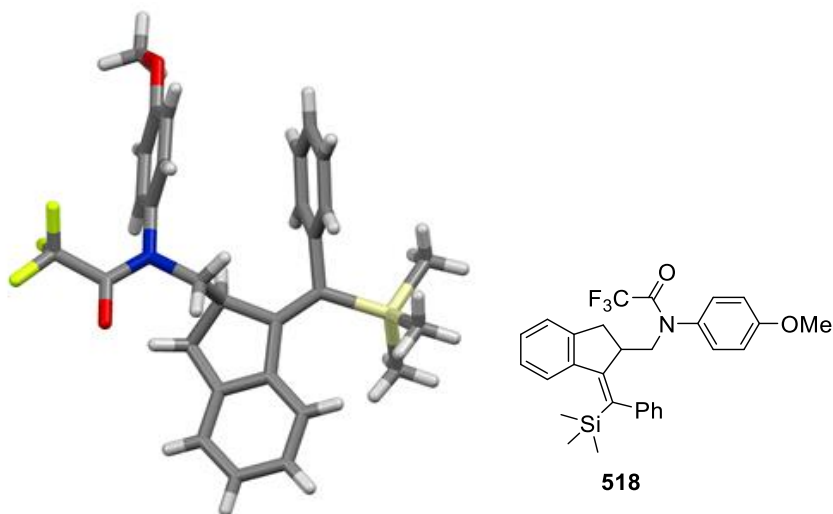
chemical formula	$\text{C}_{31}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4$	
$M_r/\text{g mol}^{-1}$	546.53	
crystal system	orthorhombic	
space group	$P 2_1 2_1 2_1$	
Unit cell dimensions	$a = 7.98050(10) \text{ \AA}$ $b = 13.9796(2) \text{ \AA}$ $c = 23.5386(3) \text{ \AA}$	$\alpha = 90^\circ$ $\beta = 90^\circ$ $\gamma = 90^\circ$
Volume	$2626.06(6) \text{ \AA}^3$	
$Z$	4	
Density (calculated)	$1.382 \text{ g cm}^{-3}$	
$F(000)$	1136	
$\mu(\text{CuK}\alpha)$	$0.892 \text{ mm}^{-1}$	
$T/\text{K}$	150(2)	
	$-9 \rightarrow 9$	
index range	$-16 \rightarrow 16$ $-28 \rightarrow 38$	
collected reflections	37652	
unique reflections	4641	
$R_{\text{int}}$	0.1394	
reflections with $I > 2\sigma(I)$	4459	
no. parameters	361	
$R(F)$ , $F > 2\sigma(F)$	0.0487	
$wR(F^2)$ , $F > 2\sigma(F)$	0.1275	
$R(F)$ , all data	0.0502	
$wR(F^2)$ , all data	0.1294	
$\Delta_r$ (min., max.) $\text{e \AA}^{-3}$	$-0.328, 0.303$	

**2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*\*,2*R*\*)-1-nitro-1-phenylhex-5-en-2-yl)acetamide (352ac)**



chemical formula	C <sub>21</sub> H <sub>21</sub> F <sub>3</sub> N <sub>2</sub> O <sub>4</sub>	
<i>M</i> <sub>r</sub> /g mol <sup>-1</sup>	422.4	
crystal system	triclinic	
space group	<i>P</i> −1	
Unit cell dimensions	<i>a</i> = 9.4635(2) Å <i>b</i> = 10.8289(2) Å <i>c</i> = 11.6493(3) Å	<i>α</i> = 114.519(2)° <i>β</i> = 107.634(2)° <i>γ</i> = 96.514(2)°
Volume	994.96(4) Å <sup>3</sup>	
<i>Z</i>	2	
Density (calculated)	1.41 cm <sup>-3</sup>	
<i>F</i> (000)	440	
<i>μ</i> (CuK <sub>α</sub> )	0.997 mm <sup>-1</sup>	
<i>T</i> /K	150(2)	
index range	−11 → 11 −12 → 12 −12 → 12	
collected reflections	14465	
unique reflections	3511	
<i>R</i> <sub>int</sub>	0.0187	
reflections with <i>I</i> > 2σ( <i>I</i> )	3130	
no. parameters	278	
<i>R</i> ( <i>F</i> ), <i>F</i> > 2σ( <i>F</i> )	0.0327	
<i>wR</i> ( <i>F</i> <sup>2</sup> ), <i>F</i> > 2σ( <i>F</i> )	0.0844	
<i>R</i> ( <i>F</i> ), all data	0.0373	
<i>wR</i> ( <i>F</i> <sup>2</sup> ), all data	0.0871	
Δ <sub>r</sub> (min., max.) e Å <sup>-3</sup>	−0.193, 0.17	

**(Z)-2,2,2-trifluoro-N-(4-methoxyphenyl)-N-((1-(phenyl(trimethylsilyl)methylene)-2,3-dihydro-1H-inden-2-yl)methyl)acetamide (518)**



chemical formula	$C_{29}H_{30}F_3NO_2Si$	
$M_r/g\ mol^{-1}$	509.64	
crystal system	triclinic	
space group	$P\ -1$	
Unit cell dimensions	$a = 10.1262(3)\ \text{\AA}$ $b = 12.1318(4)\ \text{\AA}$ $c = 12.5425(4)\ \text{\AA}$	$\alpha = 115.009(4)^\circ$ $\beta = 96.041(3)^\circ$ $\gamma = 104.045(3)^\circ$
Volume	$1316.22(8)\ \text{\AA}^3$	
Z	2	
Density (calculated)	$1.226\ \text{cm}^{-3}$	
$F(000)$	511	
$\mu(\text{CuK}\alpha)$	$1.162\ \text{mm}^{-1}$	
T/K	150(2)	
	$-12 \rightarrow 12$	
index range	$-13 \rightarrow 14$	
	$-14 \rightarrow 14$	
collected reflections	18582	
unique reflections	4623	
$R_{\text{int}}$	0.0474	
reflections with $I > 2\sigma(I)$	3884	
no. parameters	329	
$R(F)$ , $F > 2\sigma(F)$	0.0638	
$wR(F^2)$ , $F > 2\sigma(F)$	0.1751	
$R(F)$ , all data	0.0814	
$wR(F^2)$ , all data	0.1853	
$\Delta_r$ (min., max.) $e\ \text{\AA}^{-3}$	-0.378, 1.622	

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